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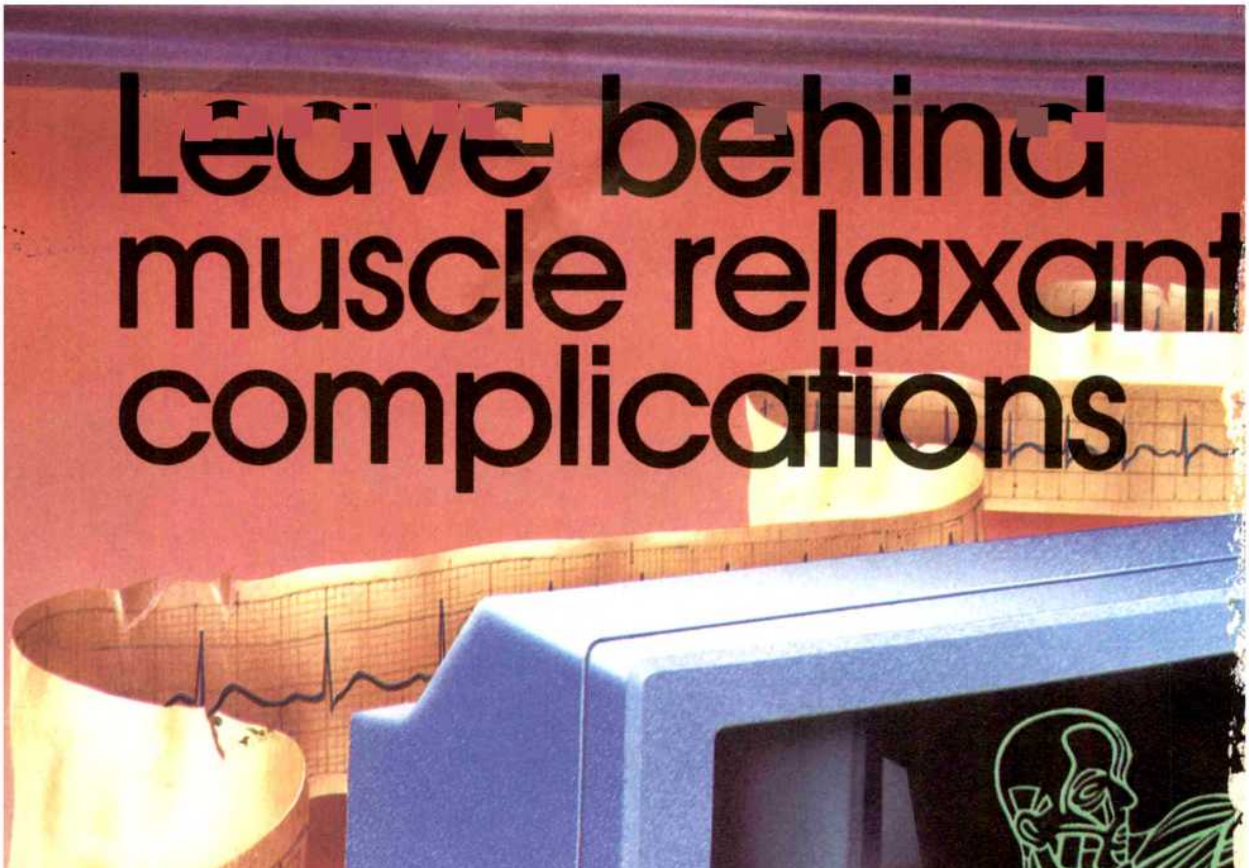
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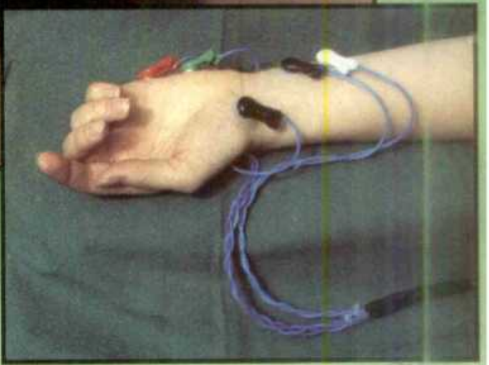

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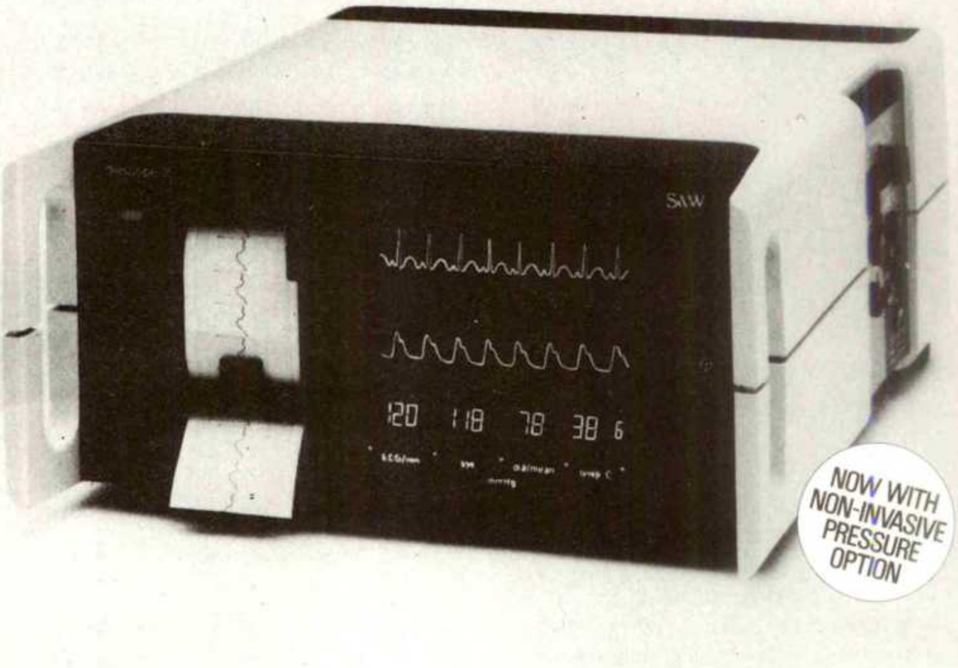

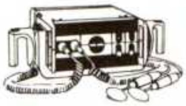

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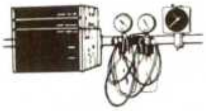

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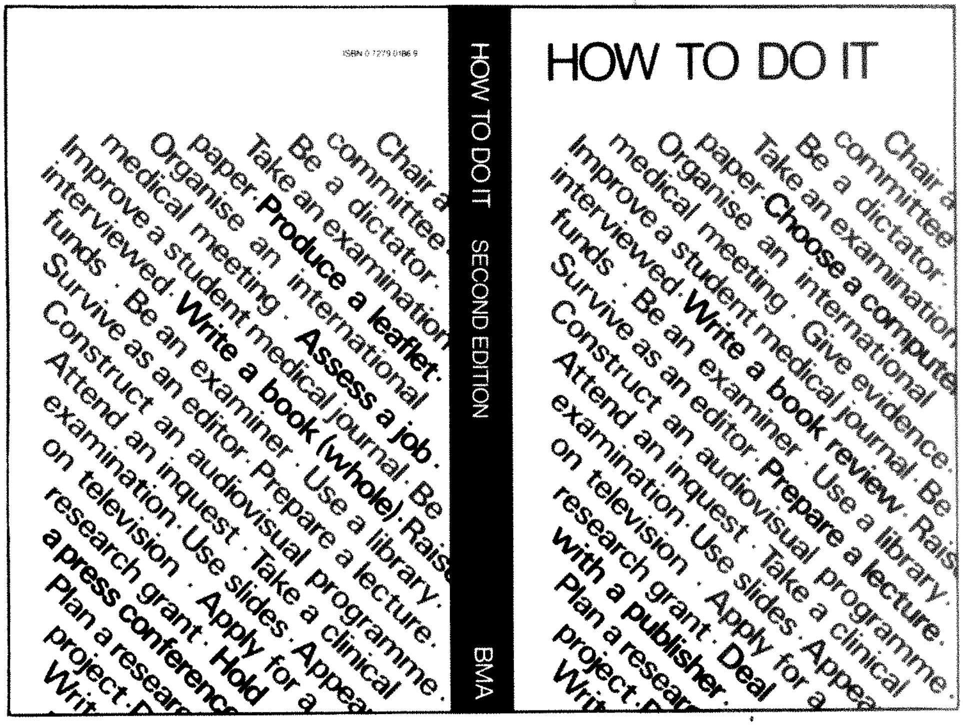

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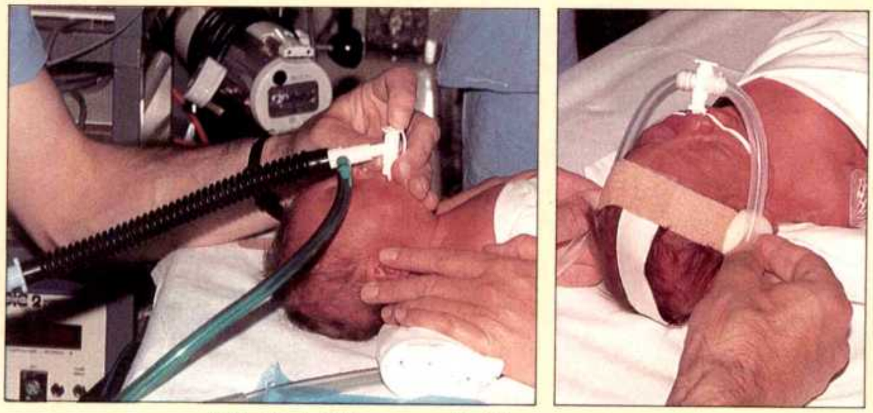

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DISPOSITION OF PROPOFOL IN PATIENTS UNDERGOING SURGERY

A Comparison in Men and Women

CP25766

N. H. KAY, J. W. SEAR, J. UPPINGTON, I. D. COCKSHOTT AND E. J. DOUGLAS

SUMMARY

The disposition kinetics of propofol have been determined in 12 patients (six female) receiving propofol 2.5 mg kg^{-1} for induction of anaesthesia, which was maintained with 67% nitrous oxide in oxygen and 1–1.5% halothane. Peripheral blood samples were collected at selected times up to 8 h after the injection of the drug, and whole blood propofol concentrations determined by HPLC with fluorescence detection. Drug concentration–time data were analysed by the non-linear regression program ELSFIT. This showed the data to be describable by a tri-exponential equation, corresponding to a three-compartment model. There were no differences in the derived kinetic indices for the male and female patients, with the exception of a greater Vd^{ss}: V^{γ} ratio in the males. The terminal half-life in the male patients was 262 min (SEM 44), and in the female patients 309 min (60). Vd^{ss} was 329 litre (67) and 313 litre (69) in male and female patients, respectively. The clearance in both groups was 1.8 litre min^{-1}. Seven out of 12 patients showed significant secondary peaks in blood propofol concentration associated with recovery from anaesthesia.

Di-isopropyl phenol (propofol) when formulated in Cremophor EL was first shown to be an effective i.v. induction agent by Kay and Rolly (1977). However, a high incidence of pain on injection, and the possible association of Cremophor-containing agents and anaphylactoid reactions, led to the development of an emulsion formulation, and the use of this formulation of propofol for the induction and maintenance of anaesthesia has been described (Cummings et al., 1984; Kay et al., 1985). Adam and colleagues (1983) have reported previously on the kinetics of single doses of the Cremophor formulation in unpremedicated gynaecological patients, while Cockshott, Briggs and Douglas (1985) have studied the disposition of the emulsion formulation, also in unpremedicated female patients.

This study compared the kinetics of a single induction dose of propofol in male and female patients premedicated with diazepam, in whom anaesthesia was maintained with halothane to supplement 67% nitrous oxide in oxygen.

PATIENTS AND METHODS

The study was approved by the local hospital ethics advisory committee and all patients gave informed consent. The 12 patients (six male) (ASA I or II; aged 27–65 yr; weighing 55–95 kg) were scheduled to undergo minor gynaecological or body surface operations. All patients had normal renal and hepatic function when assessed by routine laboratory testing. No patient was suffering from cardiac or pulmonary disease; none was receiving, or had received within the week before admission, intercurrent drug therapy known to alter hepatic blood flow or hepatic microsomal metabolizing activity.

N. H. KAY, B.SC., M.B., B.S., F.F.A.R.C.S.; J. W. SEAR, M.A., B.S.C., PH.D., F.F.A.R.C.S.; J. UPPINGTON, M.B.B.S., D.A., D.R.C.O.G., F.F.A.R.C.S.; Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford OX3 9DU. I. D. COCKSHOTT, B.SC., PH.D.; E. J. DOUGLAS, H.N.C.; Pharmacokinetics Section, Safety of Medicines Department, ICI, Pharmaceuticals Division, Macclesfield, Cheshire.

Correspondence to J. W. S.

Diazepam 10 mg by mouth was given as premedication 2 h before the induction of anaesthesia. A 14–s.w.g. cannula was inserted to a vein in the non-dominant ante-cubital fossa under local anaesthesia, and then flushed periodically with heparinized saline. A bolus induction dose of propofol 2.5 mg kg^{-1} was injected i.v. via a separate cannula in the contralateral forearm over 20 s. Anaesthesia was maintained with 1.5% halothane in a mixture of 67% nitrous oxide in oxygen. Respiration was spontaneous throughout. No other drugs, including narcotics, were given to any patient. During the surgical procedure, the electrocardiogram was monitored continuously, and the heart rate and arterial pressure recorded at 5-min intervals.

At the end of surgery the times to opening eyes on command and to giving a correct date of birth following the cessation of the nitrous oxide and halothane were recorded.

Blood sampling

Samples of venous blood (5 ml) were taken before the induction of anaesthesia and at the following times after the end of the bolus injection of propofol: 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min. Samples were collected in blood tubes containing potassium oxalate, mixed thoroughly, and cooled to +4 °C to await analysis.

Assay for propofol

Propofol concentrations in samples of whole blood were measured after extraction into cyclohexane by a high-pressure liquid chromatographic method with fluorescence detection (in preparation). The method has a limit of detection of approximately 2 ng nl^{-1}, and the interbatch coefficient of variation of the assay over the concentration range observed in this study was approximately 8%.

Kinetic analysis

After determination of preliminary initial estimates for the exponents and constants using the program STRIPE (Johnston and Woollard, 1983), the data could be described by a poly exponential function using the non-linear regression program ELSFIT (Peck et al., 1984). Weighting of the data was based on the Elsfit Version 3.0 variance model. Choice of a tri-exponential model was based on the Schwarz criterion, and by visual assessment of the residuals of the measured concentrations from the lines of best fit. Because of the transitory nature of the secondary peaks in whole blood drug concentrations, it was felt justifiable to use a poly-exponential function to describe the changes in concentration with time. Kinetic indices were determined using formulae defined by Wagner (1976).

Statistical methods

Demographic details were compared by Student's *t* test; recovery indices by Student's *t* test on log transformed data to overcome positive skewness; and the kinetic constants and exponents, and derived variables by the Mann–Whitney *U* test.

RESULTS

Anaesthesia was uneventful in all 12 patients, the arterial pressure and heart rate being maintained to within 15% of their pre-induction values. Pain on the administration of propofol was noted in five of the 12 patients. The duration of anaesthesia (taken to cessation of nitrous oxide and halothane) ranged from 18 to 66 min. There was no difference between the groups with respect to the duration of anaesthesia (31.0 (SEM 4) min in female patients; 44.0 (6) min in the male patients).

Whole blood concentrations of propofol decreased in a curvilinear manner with seven of 12 patients showing significant secondary peaks associated with awakening (fig. 1). The drug concentrations at this time were in the approximate range 100–1000 ng ml^{-1} and the magnitude of the peak ranged up to a 100% increase in the propofol concentration. These increases were analytically significant (greater than 2SD for the assay at the individual concentrations).

Determination of the area under the curve (AUC_{0-480}) using the trapezoidal approximation revealed no differences between male and female patients. The individual constants and exponents, and the derived pharmacokinetic variables are shown in table I.

There were comparable values for the three half-lives in the two groups of patients, and no differences were seen in systemic drug clearance. Correlation analysis showed no relationship between age ($r = 0.381$), or body weight ($r = 0.156$) and systemic clearance. However, a significant correlation ($r = 0.732$; $P < 0.01$) existed between the $AUC_{0-\infty}$ and body weight.

The initial volume of distribution (V_1) and the apparent volume of distribution during the

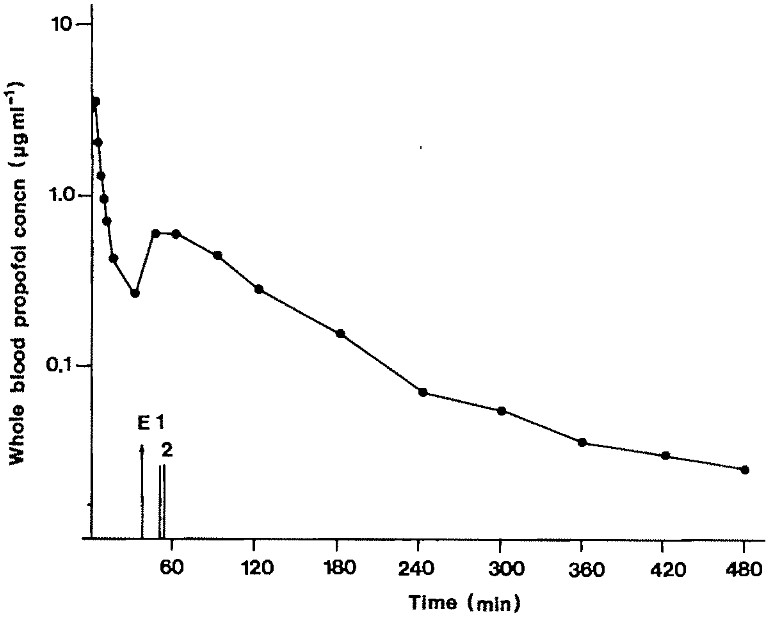

FIG. 1. Plot of the whole blood propofol concentration–time curve following the i.v. administration of 2.5 mg kg^{-1} to a female patient. The secondary peak in the drug concentration occurs at the time of awakening. E = End of anaesthesia, taken as cessation of halothane and nitrous oxide; 1 = patient opens eyes to command; 2 = patient able to give correct date of birth on command.

TABLE I. *Area under the curve (AUC) between 0 and 480 min by the trapezoidal approximations and the derived pharmacokinetic parameters for six male and six female patients following a single dose of propofol 2.5 mg kg^{-1} (mean ± SEM). Notation according to Hull (1979). No significant differences were found between patient groups*

	Female	Male
AUC_{0-480} (µg min ml^{-1})	89.8 (16.6)	100.5 (9.0)
A (µg ml^{-1})	4.73 (1.09)	4.17 (0.71)
α (min^{-1})	0.324 (0.026)	0.343 (0.059)
B (µg ml^{-1})	0.80 (0.19)	0.78 (0.14)
β (min^{-1})	0.016 (0.0011)	0.0127 (0.001)
C (µg ml^{-1})	0.086 (0.026)	0.115 (0.025)
γ (min^{-1})	0.0026 (0.0003)	0.0030 (0.0005)
$AUC_{0-\infty}$ (µg min^{-1} ml^{-1})	99.5 (18.2)	109.8 (8.8)
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.2 (0.2)	2.4 (0.4)
$T_{\frac{1}{2}}^{\beta}$ (min)	44.9 (4.0)	56.0 (4.0)
$T_{\frac{1}{2}}^{\gamma}$ (min)	309 (60)	262 (44)
V_1 (litre)	36.1 (10.3)	42.3 (5.9)
V^{γ} (litre)	801 (168)	708 (153)
Vd^{ss} (litre)	313 (69)	329 (67)
Cl (litre min^{-1})	1.80 (0.22)	1.81 (0.15)
Cl (ml min^{-1} kg^{-1})	29.1 (4.6)	23.6 (2.3)

elimination phase (V^{γ}) were similar in the two groups of patients. Neither showed any correlation with body weight. The apparent volume of distribution at steady state (Vd^{ss}), calculated according to Wagner (1976) using the derived constants and exponents, was similar in the two groups, although the ratio Vd^{ss}: V^{γ} was significantly greater in the male patients ($P = 0.021$).

Recovery to eyes opening on command, and to giving correct date of birth occurred in the concentration ranges 0.22–1.03 µg ml^{-1} and 0.21–0.98 µg ml^{-1}, respectively.

DISCUSSION

This paper describes the disposition of the new formulation of diisopropyl phenol (propofol) in spontaneously breathing male and female patients undergoing body surface surgery. The data are comparable to those recently reported by Cockshott, Briggs and Douglas (1985) for female patients undergoing minor gynaecological surgery. However, there are significant differences from the kinetics reported for the Cremophor formulation when given either by single bolus injection or continuous i.v. infusion (Prys-Roberts, Sear and Adam, 1981; Adam, Kay and Douglas, 1982; Adam et al., 1983).

Alterations in disposition kinetics could be the result of changes in drug bioavailability if clearance occurs on the first pass through the lungs. In addition, studies by von Dardel and colleagues (1983) and Fee and co-workers (1984) have shown differences in the kinetics of diazepam when formulated in an oil in water emulsion (Diazemuls; Kabi Vitrum Ltd); or propylene glycol (Valium; Roche Products Ltd). However, this has not been confirmed by more recent preliminary data from Naylor and Burlingham (1985). The longer terminal half-life (overall mean 286 min) may reflect the true delineation of a further elimination phase in the metabolism of propofol. Comparison of the present study with that of Adam and associates (1983) shows similar values for the α- and β-phase half-lives. The accuracy of our γ-phase half-life must be limited by the sampling period—which was only 1.5–2, not the accepted 3 or more, times the terminal elimination half-life. Indeed, a longer half-life of 502 min has been described in volunteers, when sampling was continued for 12 h (Cockshott, 1985).

The systemic clearance of propofol, 1.80 litre min^{-1}, is similar to that described for hepatic blood flow during halothane anaesthesia (Gelman, 1975, 1976; Andreen et al., 1981). However, the clearance was significantly less than that reported by Adam and colleagues (1983) in unpremedicated subjects receiving the Cremophor-formulated drug alone for anaesthesia .

Recent studies by Reilly and associates (1984), have shown that halothane will decrease the systemic drug clearance of propranolol by decreasing hepatic blood flow and intrinsic hepatic enzyme activity. Comparing the data from this study with those from volunteers (Schüttler, Stockel and Schwilden, 1985; Simons et al., 1985) shows the clearance during halothane anaesthesia to be about 80% of that in volunteers. This reduction is similar to that found by Reilly and colleagues (1984) in the dog. However, it should be remembered that the period of exposure of our patients to halothane was unlikely to cause a significant change in overall clearance unless it had a very large, or persistent, effect.

Our determinations of V_1 and Vd^{ss} may both be subject to over estimation. Although the curve-fitting indicates an initial distribution half-life of approximately 2 min, this is similar to the duration of the first sampling period. The influence of the initial sampling regimen on the determination of V_1 has been described elsewhere (Chiou, 1980). Similarly, drug distribution is dependent on the active drive force, namely the arterial drug concentration. Calculation of Vd^{ss} based on venous sampling data may result in overestimation (Chiou, 1982).

In this study, there were no differences in the kinetics of propofol between male and female patients, except for the ratio $Vd^{ss}:V^{\gamma}$. Overall, the value for this ratio was low (0.34–0.58), reflecting the persistence of a significant fraction of the injected dose of this highly lipophilic drug in a poorly perfused tissue compartment, such as fat. As expected, the ratio was greater in male than female patients as a result of the greater percentage body fat of the latter group (Greenblatt et al., 1980).

The whole blood propofol concentrations estimated from the best-fit profiles at awakening were less than those reported by Adam, Kay and Douglas (1982). However, in that study no other anaesthetic agent was administered to the patients; it is likely, therefore, that recovery in our patients was dependent on the elimination of the volatile agent rather than of propofol. The increases in drug concentrations at awakening have been seen with other lipophilic i.v. anaesthetic agents, such as fentanyl (McQuay et al., 1979), thiopentone (Morgan et al., 1981) and Althesin (Sear, 1981). Becker and his colleagues (1976) noted that, in the case of fentanyl, carbon dioxide response curves were at their lowest at approximately the time the patients entered the recovery room. This coincided with the occurrence of the secondary peaks in plasma fentanyl concentration.

What explanation can be offered for these increases in drug concentration? Elfstrom (1979) has commented on the alterations in cardiac output and regional blood flow that occur during recovery from anaesthesia. These may lead to the release of drug from lipid tissues. Our data do not allow clarification as to whether the propofol was derived from local tissues adjacent to the sampling site, or from a whole body increase in drug concentrations. Certainly the alphaxalone peaks seen after the infusion of Althesin (Sear, 1981) were detectable in arterial blood samples, and so probably support the latter hypothesis.

In summary, there was a very rapid distribution and rapid elimination of propofol when it was administered by bolus dose for induction of anaesthesia. The high systemic clearance should make this drug suitable for use by continuous infusion. However, the development of regimens to achieve target drug concentrations must take account of the influence of concurrently administered anaesthetic agents, or other drugs known to affect hepatic blood flow or intrinsic enzyme activity.

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Br. J. Anaesth. (1986), 58, 1080–1084

DOSE REQUIREMENTS OF PROPOFOL BY INFUSION DURING NITROUS OXIDE ANAESTHESIA IN MAN

I: Patients Premedicated with Morphine Sulphate

K. R. SPELINA, D. P. COATES, C. R. MONK, C. PRYS-ROBERTS,
I. NORLEY AND M. J. TURTLE

SUMMARY

The study was performed to determine the ED_{50} and ED_{95} of a continuous infusion of the emulsion formulation of propofol during 67% nitrous oxide anaestheisa in 57 patients premedicated with morphine sulphate 0.15 mg kg^{-1}. Anaesthesia was induced with propofol 2 mg kg^{-1}, and maintained before incision with a fixed-rate infusion of propofol to supplement nitrous oxide. The response to the first surgical incision, made at least 30 min after induction of anaesthesia, was observed. The ED_{50} was 53.5 μg kg^{-1} min^{-1} and the ED_{95} was 112.2 μg kg^{-1} min^{-1}. At the time of the first surgical incision, the venous whole blood concentrations of propofol at the ED_{50} and ED_{95} infusion rates (EC_{50} and EC_{95}) were 1.66 μg ml^{-1} and 3.39 μg ml^{-1}, respectively. The satisfactory maintenance of anaesthesia provided by nitrous oxide supplemented with propofol was associated with haemodynamic stability and rapid, uncomplicated recovery.

To allow meaningful comparison of the pharmacological effects of different i.v. anaesthetics given by continuous infusion, it is necessary to define a measure of potency in a manner similar to that established for volatile anaesthetics. The minimum infusion rate (MIR) was introduced (Sear and Prys-Roberts, 1979) to define the ED_{50} of an i.v. anaesthetic which suppressed movement in response to the surgical incision. Unlike its corollary, the minimum alveolar concentration (MAC) of an inhalation anaesthetic, MIR does not necessarily equate with the concentration of the anaesthetic in the blood. Both MAC and MIR should be determined under steady-state conditions of anaesthesia and only an approximation is made by determining the response, or lack of response, to the initial surgical incision when a state of stable anaesthesia, as opposed to a true pharmacological steady-state, has been established.

For patients premedicated with morphine sulphate and breathing 67% nitrous oxide in oxygen, the MIR of the Cremophor EL formulation of propofol was determined to be 51.3 μg kg^{-1} min^{-1} (Prys-Roberts, Sear and Adam, 1981). Different induction pharmacodynamics have been reported (Cummings et al., 1984) for the newer emulsion formulation of propofol (1% 2,6 di-isopropyl phenol in an emulsion of 10% soya bean oil, 2.25% glycerol and 1.2% egg phosphatide) as compared with the formulation in Cremophor EL. Therefore, as a prelude to pharmacological studies of continuous infusion anaesthesia, we have determined the ED_{50} and ED_{95} for propofol in patients premedicated with morphine sulphate and breathing nitrous oxide.

PATIENTS AND METHODS

Each patient gave informed consent to participate in the study which had been approved by both the Committee on Safety of Medicines and the Hospital Ethical Committee. Healthy patients (ASA I or II) scheduled for body surface surgery were premedicated with morphine sulphate 0.15 mg kg^{-1} i.m. 1 h before anaesthesia. The

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K. R. SPELINA, M.D., F.F.A.R.C.S.; D. P. COATES, M.B., B.S., F.F.A.R.C.S.; C. R. MONK, M.B., CH.B., F.F.A.R.C.S.; C. PRYS-ROBERTS, M.A., D.M., PH.D., F.F.A.R.C.S.; I. NORLEY, M.SC., M.B., B.S., F.F.A.R.C.S.; M. J. TURTLE, M.B., B.S., F.F.A.R.C.S.; Sir Humphry Davey Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW.

TABLE I. *Clinical data of 57 patients receiving propofol by infusion. Values for age and weight are expressed as mean ± SD*

	Study A					Study B	
Infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)	40	50	60	70	80	54	108
n	8	8	8	8	8	9	8
Age (yr)	40.8 ±11.6	46.9 ±12.3	45.8 ±13.3	39.9 ±12.3	45.4 ±9.9	49.7 ±7.5	47.3 ±5.3
Weight (kg)	69.0 ±17.6	73.3 ±14.1	74.2 ±7.8	68.4 ±13.4	72.3 ±13.6	80.7 ±22.6	68.9 ±11.5
Male/Female	4/4	6/2	5/3	5/3	6/2	5/4	4/4

details of the first 40 patients are shown in table I (study A). Initially, five different rates of infusion were studied and eight patients randomly allocated to each group. We also include the response to surgical incision of 17 patients managed identically to those above, but participating in the subsequent pharmacokinetic studies: infusions of 54 or 108 $\mu g\ kg^{-1}\ min^{-1}$ were administered to nine and eight patients, respectively. Their details are shown in table I (study B). Under local analgesia, a 16-gauge cannula was placed in a forearm vein, a blood sample taken and the concentration of propofol measured (baseline). Propofol was administered from a calibrated syringe pump (Vickers Treonic: IP3) connected to this cannula; no other drugs were injected through this system.

Patients were asked to report any sensations associated with induction at the time. Anaesthesia was induced with propofol 2 $mg\ kg^{-1}$ given i.v. over 20 s. The propofol infusion of 40, 50, 54, 60, 70, 80 or 108 $\mu g\ kg^{-1}\ min^{-1}$ was started immediately after induction. The infusion supplemented anaesthesia maintained with 67% nitrous oxide in oxygen inhaled from a face mask and Lack breathing system. An oral Guedel airway was used when appropriate. The surgical incision occurred at least 30 min after induction (median 35 min, range 30–105 min) and a sample of peripheral venous blood was obtained simultaneously from either an external jugular vein or a cubital vein in the arm contralateral to the infusion. The response to the incision was observed and the patients categorized as "movers" or "non-movers". Subsequently, anaesthesia was adjusted, as clinically appropriate, by incremental doses or an altered rate of infusion of propofol. One patient, who had received an infusion of 40 $\mu g\ kg^{-1}\ min^{-1}$ before incision, required halothane during the subsequent anaesthetic maintenance. The arterial pressure (Dinamap 845, Critikon) and electrocardiogram were monitored in all patients throughout the study.

Nitrous oxide and the infusion of propofol (if still in progress) were discontinued simultaneously at the end of surgery. Oxygen-enriched air was administered by face mask until recovery was complete. The times from the discontinuation of anaesthesia to opening the eyes to command and to correct recall of birthdate were recorded. Patients were questioned 1 h after recovery from anaesthesia, and on the first day after operation, to assess recall of events before, during and after anaesthesia. The vein used for the administration of propofol was examined at these times. Whole blood propofol concentrations were determined by high pressure liquid chromatography with fluorescence detection at ICI Pharmaceuticals Division, Cheshire. Probit line analysis (Litchfield and Wilcoxon, 1949) was used to determine the ED_{50} and ED_{95}. Linear regression analysis was used to assess correlations between the whole blood concentration of propofol at incision and the rate of infusion, and the log-transformed recovery times and the total dose of propofol given.

TABLE II. *Sensations reported by 57 patients during induction of anaesthesia with propofol 2 mg kg^{-1} i.v.*

Sensation	No. patients
Pain	
None	43
Mild	10
Severe	4
Other	
Cold/numbness	14
Warmth in vein	2
Tingling	
Arm	2
Face	2

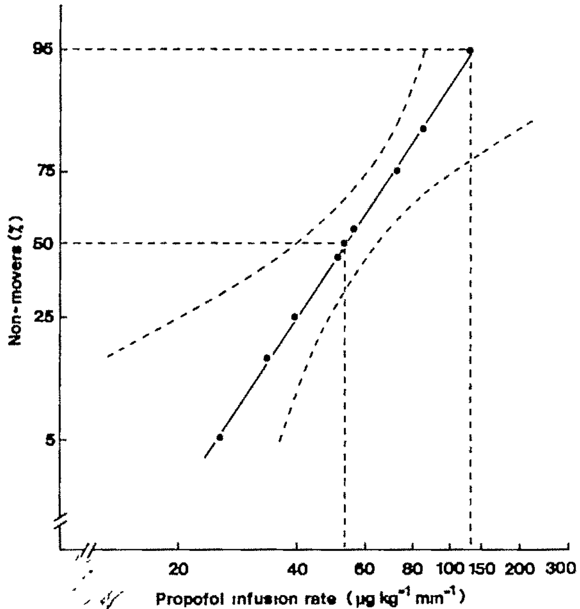

FIG. 1. Probit plot of patients moving or not moving as a function of propofol infusion rate (as log µg kg^{-1} min^{-1}). The mean probit values for each infusion rate are shown with the corresponding 95% confidence limits.

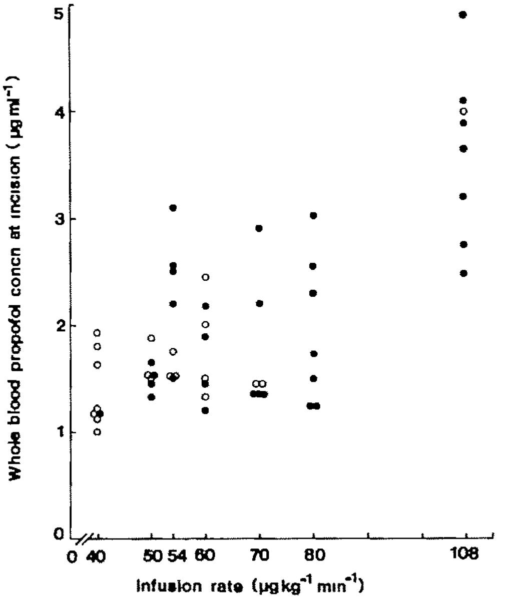

FIG. 2. Whole blood propofol concentration (µg ml^{-1}) as a function of propofol infusion rate (µg kg^{-1} min^{-1}) in 53 patients. Open circles indicate patients who moved, closed circles indicate patients who did not move in response to the initial surgical incision. The regression is given as: $y = 0.878 + 0.029x$ ($r^2 = 0.51$, $P < 0.001$).

RESULTS

Pain in the arm, at the time of induction was reported by 25% of the patients. The sensations experienced are shown in table II.

Figure 1 shows the relationship between infusion rate and suppression of movement in response to the initial surgical stimulus. From this log-dose probit plot, the ED_{50} was determined to be 53.5 µg kg^{-1} min^{-1} (95% confidence limits: 39.9–63.0 µg kg^{-1} min^{-1}) and the ED_{95} to be 112.2 µg kg^{-1} min^{-1} (85.6–306.2 µg kg^{-1} min^{-1}).

Assays of baseline blood samples for propofol concentration were negative. There was a strong

TABLE III. *Duration of anaesthesia and surgery and the total dose of propofol given (mean ± SD); times from end of anaesthesia to eye opening and recall of birthdate (median and range) in 39 patients each receiving propofol by continuous infusion at one of five different rates to supplement anaesthesia maintained with 67% nitrous oxide. (*The eighth patient in the 40 µg kg^{-1} min^{-1} group received halothane and is not included)*

	Infusion rate (µg kg^{-1} min^{-1})				
	40	50	60	70	80
Patients in group	7*	8	8	8	8
Anaesthesia	78.29	95.63	76.88	82.00	82.23
(min)	±21.54	±24.34	±28.37	±32.47	±22.42
Surgery	31.5	56.0	31.4	44.4	45.3
(min)	±13.7	±26.2	±15.5	±26.8	±23.5
Total dose of propofol	403.0	472.5	489.5	555.4	547.8
(mg)	±78.2	±89.4	±133.6	±263.7	±90.6
Eyes open	4.74	4.35	5.51	5.97	5.19
(min)	(1–18)	(4–8)	(4–9)	(4–12)	(3–14)
Correct birth date	7.33	5.89	7.81	7.43	6.57
(min)	(4–19)	(5–9)	(6–11)	(5–15)	(4–18)

correlation ($r^2 = 0.51$, $P < 0.001$) between whole blood propofol concentration and the infusion rate at the time of incision (fig. 2). The mean whole blood propofol concentrations at the ED_{50} and ED_{95} infusion rates were 1.67 μg ml^{-1} and 3.38 μg ml^{-1}, respectively.

Details of the duration of anaesthesia, surgery and recovery are given in table III. There was no correlation between the total dose of propofol given (mg kg^{-1}) and the times either to response to command, or to recall of birth date.

All patients were haemodynamically stable throughout anaesthesia and no significant arrhythmias occurred. No patient could recall any event during anaesthesia or surgery. There was no phlebitis or thrombosis of the vein used for the administration of the propofol in any patient within 24 h of the infusion.

DISCUSSION

The introduction of a new formulation for propofol as an aqueous emulsion raised numerous questions concerning dose requirement for induction and maintenance of anaesthesia. Cummings and colleagues (1984) found that the dose of propofol required to induce anaesthesia was about 25% greater than that for the Cremophor formulation, suggesting a formulation-dependent difference in the distribution of the drug.

In order to determine the dose requirement for continuous infusion anaesthesia, we have used the probit analysis approach (Litchfield and Wilcoxon, 1949) under exactly the same conditions as those in which the maintenance infusion rates of Althesin or methohexitone were determined (Sear et al., 1983). In all these studies, the simple strategy of a single induction dose followed by a predetermined continuous infusion has been used. While this strategy has the disadvantage that blood concentrations of the appropriate drug decrease to below the desired concentration after the peak associated with the induction dose, our subsequent studies (Prys-Roberts, Cockshott and Douglas, unpublished observations), of which the data at 54 and 108 μg kg^{-1} min^{-1} form a part, have indicated that, at the time of surgical incision in those patients, the whole blood propofol concentrations were within 5% of those subsequently achieved during further periods of anaesthesia up to 120 min.

The ED_{50} for propofol determined in the present study (53.5 μg kg^{-1} min^{-1}) was only marginally higher than that for the Cremophor EL formulation (Prys-Roberts, Sear and Adam, 1981). However, the MIR in the previous study was not determined by the same method of probit analysis, but by a bracketing technique in which the infusion rate required just to suppress movement in response to surgery was averaged for nine patients.

The ED_{50}/ED_{95} concept also allows comparison of different anaesthetics given by infusion under comparable conditions. Values for Althesin and methohexitone have been reported following premedication with either morphine or diazepam (Sear et al., 1983), and the influence of age on these relationships has also been described (Sear, Prys-Roberts and Phillips, 1984). The new formulation of propofol is marginally less potent than methohexitone at the ED_{50}, but the slope of the dose–response curve for propofol is rather flatter, and the 95% confidence limits at the ED_{95} rather wider. Nevertheless the data provide a satisfactory basis for further haemodynamic and pharmacokinetic studies of infusions of propofol (Coates et al., 1986; Monk et al., 1986), and target infusion rates and blood concentrations for studies of open-loop computer controlled infusions of propofol. We have not been able to determine a correlation with age in the present study because of the relatively small numbers involved, but hope to accumulate sufficient data in subsequent studies to allow a comparison with the data for Althesin or methohexitone (Sear, Prys-Roberts and Phillips, 1984).

The times to response to command and to correct recall of birth date were comparable to values observed with a number of anaesthetics given for short surgical procedures (Craig, Cooper and Sear, 1982), even though the duration of anaesthesia in the present study was of the order of 1–2.5 h. The lack of correlation between the total dose of propofol and the chosen indicators of recovery confirms the findings of Kay and co-workers (1985), who also found recovery to be considerably faster when the emulsion formulation of propofol was used to supplement nitrous oxide, compared with patients who received Althesin. Many of our patients, particularly those who had undergone general anaesthesia in the past, remarked on the "clear headedness" of their recovery. The general impression of rapid recovery was reinforced by the opinions of the recovery room staff.

The emulsion formulation of propofol provides a valuable addition to the small number of drugs currently available for infusion anaesthesia. Its clinical effects are predictable, consistent and associated with a rapid recovery.

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We are grateful to Dr R. D. Stark and Miss Sue Binks of I.C.I. Pharmaceuticals Division, Macclesfield for support of the study and supplies of propofol, and to Dr I. Cockshott and Mr E. J. Douglas for the analyses of blood samples for propofol concentration. We would also like to thank those surgeons in the Bristol Royal Infirmary who have allowed us to study patients in their care.

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A METHOD FOR PRODUCING CONSTANT PLASMA CONCENTRATIONS OF DRUGS

Application to Methohexitone

T. J. McMURRAY, F. P. ROBINSON, J. W. DUNDEE, J. G. RIDDELL AND E. McCLEAN

In 1968, Kruger-Theimer described the ideal i.v. drug input required to produce rapidly, and maintain, constant plasma concentrations of a drug: namely, the use of a single loading dose in combination with an infusion the rate of which declines exponentially towards that required to maintain the desired plasma concentration. This concept was further studied and developed by Vaughan and Tucker (1976). An exponentially decreasing infusion concentration can be produced by the mixing of two solutions of different concentration, but application of this theoretical knowledge has been hampered by the lack of a simple device which would produce this infusion with sterile solutions.

Recently, Riddell and colleagues (1984) described a method which seemed to overcome this problem. This consisted of a regimen in which a dilute solution of a drug was infused through a fine-bore needle, at a constant rate, to a sealed rigid mixing chamber containing a more concentrated solution of the drug. Infusion through the fine-bore needle created sufficient turbulence to ensure adequate mixing and the resultant exponentially decreasing mixture was displaced through a second needle. We report here the application of these principles in i.v. anaesthesia, using a methohexitone infusion in combination with 67% nitrous oxide in oxygen.

SUMMARY

A delivery system in which a dilute infusion of methohexitone is continuously added to a smaller volume of more concentrated solution has been used to infuse exponentially decreasing drug concentrations at a constant rate of infusion. The constants for calculation of concentrations and infusion rate are described. It was possible to achieve and maintain the target plasma concentration required to produce anaesthesia in conjunction with nitrous oxide in oxygen. Methohexitone is the only available drug suitable for this technique, but it requires frequent opioid supplementation and is not the ideal drug for such a technique.

PATIENTS, MATERIALS AND METHODS

Preliminary studies

An initial study was carried out in patients presenting for body surface operations. Following an induction dose of 1.6 mg kg^{-1}, methohexitone was administered intermittently in association with nitrous oxide in oxygen. The findings in 50 unpremedicated patients showed a skew distribution (fig. 1) similar to that found by Wright and colleagues (1984) for propofol. On the basis of figure 1, the median dose requirement was determined as 154 μg kg^{-1} min^{-1}. Fractions of this dose (supplemented when necessary) were infused to 40 patients (four groups of 10 patients per group) and the following results obtained. When given alone, methohexitone 77 μg kg^{-1} min^{-1} was totally inadequate, 115 μg kg^{-1} min^{-1} was effec-

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T. J. McMurray, M.D., F.F.A.R.C.S.; F. P. Robinson, M.B., F.F.A.R.C.S.; J. W. Dundee, M.D., PH.D., F.R.C.P., F.F.A.R.C.S.; J. G. Riddell, M.D., B.SC., M.R.C.P.; E. McClean, F.I.M.L.T.; Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland.

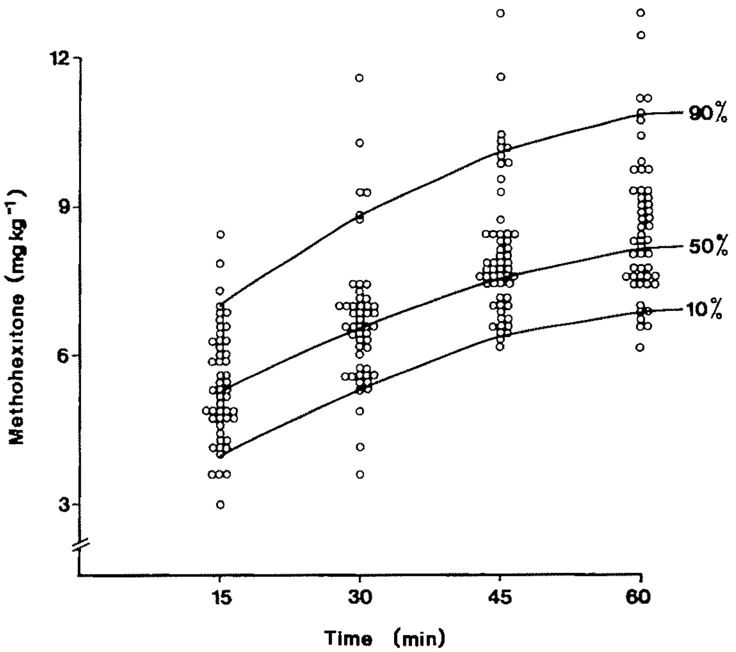

FIG. 1. Distribution of total methohexitone dosage in 50 unpremedicated patients who received incremental dosage following an initial dose of 1.6 mg kg^{-1}.

tive in 40% of patients, 154 $\mu g\ kg^{-1}\ min^{-1}$ was effective in 90%, and 192.5 $\mu g\ kg^{-1}\ min^{-1}$ was required to produce anaesthesia in 100%.

Later, pharmacokinetic studies were carried out following an initial dose of 1.6 mg kg^{-1} followed by an infusion of 192.5 $\mu g\ kg^{-1}\ min^{-1}$ which was continued for 90 min. Plasma samples were taken at frequent intervals and the methohexitone concentration determined using a modification of the high pressure liquid chromatographic technique developed for estimation of thiopentone (Toner et al., 1979) with methitural as internal standard. The coefficient of variation was less than 5% over the range of plasma concentrations studied. Pharmacokinetic parameters relating to the plasma concentrations (including post-infusion data) were derived using a non-linear curve fitting programme (NONLIN) (Meltzer, Eyring and McEwan, 1974). A weighting factor inversely proportional to the plasma concentration was taken into account. Results (table I) were similar to those of Breimer (1976), except that we found a lower initial volume of distribution (Dundee and McMurray, 1984; McMurray et al., 1984).

During the above studies, plasma samples were drawn at intervals in 28 unpremedicated patients to establish the effective concentration of methohexitone required for satisfactory anaesthesia. This averaged 10 $\mu g\ ml^{-1}$.

Materials

The apparatus consists of a 250-ml bottle containing dilute methohexitone, connected by means of a vented i.v. giving set, a peristaltic pump and a 27-swg needle, to a 50-ml multi-dose

TABLE I. *Mean values of pharmacokinetic data for methohexitone*

	V^{α} (litre kg^{-1})	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	$T_{\frac{1}{2}}^{\beta}$ (min)
This study	0.23	0.0415	0.061	0.02	108
Breimer (1976)	0.29	0.0425	0.056	0.02	96

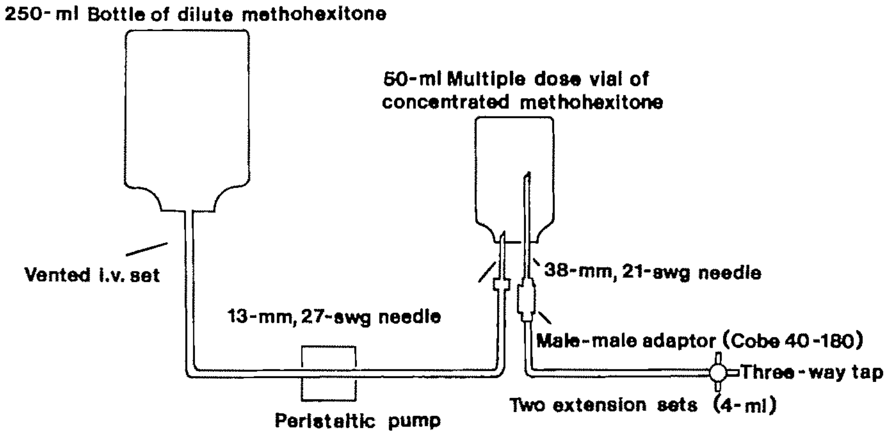
250-ml Bottle of dilute methohexitone
50-ml Multiple dose vial of concentrated methohexitone
Vented i.v. set
38-mm, 21-swg needle
13-mm, 27-swg needle
Male-male adaptor (Cobe 40-180)
Three-way tap
Two extension sets (4-ml)
Peristaltic pump

FIG. 2. Schematic representation of method of delivery of solution of exponentially decreasing concentration.

vial of more concentrated methohexitone. This chamber is connected to the patient via a 21-swg needle and two extension sets with a total capacity of 4 ml (fig. 2).

The equations used to predict the concentrations in the two chambers, the loading dose and infusion rate were as follows:

$$r = k_{21} . V_{30} \qquad (1)$$

$$M_{1t} = V . C_{1t} \qquad (2)$$

$$M_{40} = M_{1t} \frac{k_{10}\, V_{40}}{k_{21} . V_{30}} \qquad (3)$$

$$M_{30} = M_{1t} \frac{k_{12} + k_{10}}{k_{21}} . \qquad (4)$$

The infusion rate (r) equals the product of k_{21} for methohexitone and the volume of the "concentrated" chamber (V_{30}). The loading dose M_{1t} equals the product of the initial volume of distribution for methohexitone (V^{α}) and the target concentration (C_{1t}). Equations (3) and (4) relate the masses of drug in the dilute chamber (M_{40}) and concentrated chamber (M_{30}) to the volumes of these chambers and other pharmacokinetic constants for methohexitone. A detailed analysis of the derivation of these formulae has been reported by Riddell and colleagues (1984).

The initial volume of distribution plays an important role in determining the loading dose and concentrations in the two chambers. It will be seen from table I that our findings and those of Breimer (1976) differ in this respect. Plasma concentrations using these two sets of constants have been reported by Dundee and McMurray (1984), who found that the target concentration was more easily achieved by using the mean V^{α} of the two studies (0.26).

The calculated concentrations for a 70-kg subject were: dilute chamber—1910 mg in 250 ml (0.76%); concentrated chamber—910 mg in 50 ml (1.82%).

The concentration of drug in the dilute chamber was obtained by preparing a 1% solution in 250 ml from which 59 ml was removed and replaced by an equal volume of water. The concentrated chamber was prepared by withdrawing 4.5 ml from 50 ml of 2% solution and replacing with 4.5 ml of water. The tubing between the concentrated and the dilute bottles was primed from the latter. As methohexitone produces dose-related excitatory effects (Barron and Dundee, 1967), the loading dose of 180 mg was divided by priming the giving set from the concentrated bottle to the patient with 4 ml of 2% solution and the remainder was administered as a bolus over 20 s into a freely-running infusion. The infusion rate was 60 ml h^{-1} (the product of k_{21} and V_{30}) and, therefore, the total loading dose was given over 4 min.

Patients

Only fit subjects who had agreed to repeated blood sampling were included in the study. Each was scheduled for elective body surface surgery. The concentrations in the two chambers and the loading dose were calculated for the ideal 70-kg patient and administered to each subject regardless of weight. If, on clinical grounds, using the criteria of Savege and co-workers (1975), anaesthesia appeared to be inadequate, increments of fentanyl 25 μg were given.

Arterial pressure and heart rate were measured at frequent intervals throughout each procedure. The depth of respiration, as shown by movements of the chest wall or reservoir bag, was assessed carefully and respiration assisted or controlled if, on clinical grounds, there was any suspicion of respiratory depression. As it would not have been justified, on ethical grounds, to have an indwelling arterial catheter in these patients, measurements of arterial blood-gas tensions were not obtained routinely, but samples were taken in some patients when required. A capnograph was available for a few of the studies, but this necessitated tracheal intubation under local anaesthesia (aided by a small dose of suxamethonium).

All patients were visited on several occasions on the 2nd–3rd days after operation, when evidence of recall of intraoperative procedures was sought.

RESULTS

Figure 3 gives the actual concentrations delivered by the apparatus over 2 h. In this it is compared with a "simplified" method in which 1 % and 2 % solutions were "infused" at a rate of 50 ml h^{-1}. This latter delivered too high a concentration and it was not used clinically.

The scatter of plasma concentrations achieved over 60 min in 12 patients is shown in figure 4. These mostly fell within the desired range, except for some early low values and three which exceeded 13 μg ml^{-1} (two patients).

A clinical impression was formed that, in some patients, anaesthesia tended to become "deeper" than desired. This presented as respiratory depression which could not be attributable to fentanyl. It rapidly responded to stopping the infusion temporarily. It was always possible to stop the infusion at 60 min, even if the operation continued for a further 15 min. On occasions, recovery was more delayed than expected. In one such patient $T_{\frac{1}{2}}^{\beta}$ during recovery was 7–8 h.

No patient had any recall of events during operation.

Arterial pressure was well maintained in all patients and, apart from tachycardia, vital signs remained stable. Respiratory depression was not a problem, except as mentioned above. The "quality" of anaesthesia with methohexitone was often unsatisfactory, particularly at the beginning when excitatory effects and hiccup were a problem. The former always responded to a small dose of fentanyl, which however did not always stop the hiccup. More than one-half the patients required fentanyl in total dose of up to 200 μg.

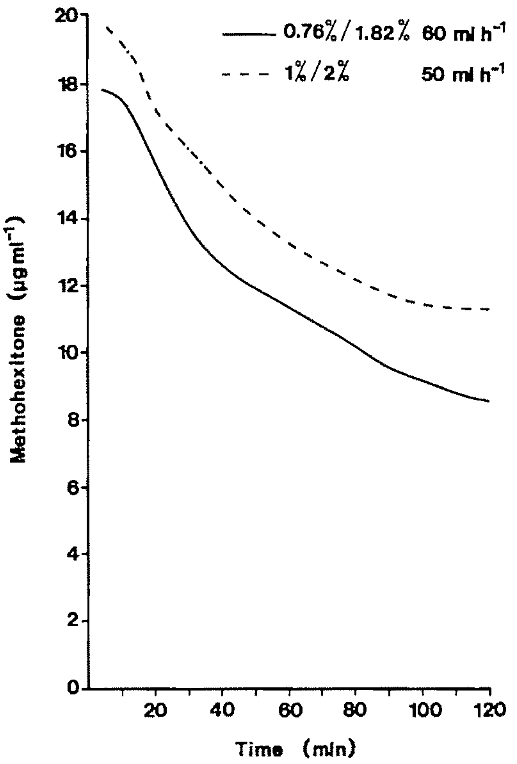

FIG. 3. Delivered concentrations of methohexitone using apparatus described in figure 2.

DISCUSSION

This was primarily a study in which we applied a pharmacokinetic principle to clinical practice. Our aim was to see if, in day-to-day operating theatre conditions, we could achieve the desired plasma concentration of methohexitone. Our choice of this drug as our infusate was based on the ability of our laboratory to carry out a large number of accurate plasma analyses of this drug. Our first studies in this field (Wright et al., 1984) were with the initial clinical preparation of propofol which was solubilized in Cremophor and which was withdrawn because of hypersensitivity reactions (Briggs, Clarke and Watkins, 1982). Although Althesin would have produced better

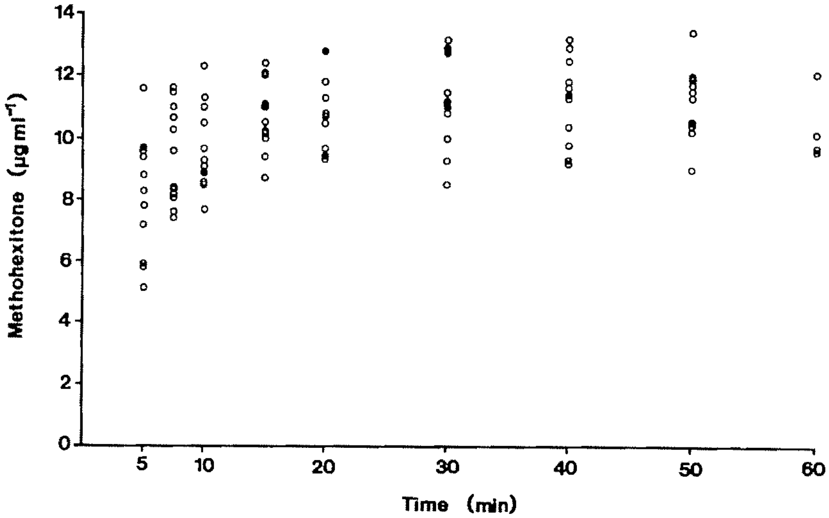

FIG. 4. Methohexitone plasma concentration (μg mg⁻¹) in 12 patients using the method of administration described in the paper. ○ = 1 patient; ● = 2 patients.

anaesthesia, we were fortunate in not selecting it as it was withdrawn during the period of the study. Etomidate causes a high incidence of excitatory effects in the absence of concomitant opioid medication and doubt has been cast on its safety after prolonged use (Ledingham and Watt, 1983; Sear et al., 1983). In view of recent pharmacokinetic studies, it was expected that thiopentone would not have been suitable for our purpose (Hudson, Stanski and Burch, 1983), having a much longer elimination half-life than methohexitone.

Methohexitone induces a high incidence of extraneous muscle movement and hiccup, particularly after the rapid administration of large doses, and for this reason the induction dose was given in divided doses. However, despite this, induction was often "bumpy", and while this usually responded to fentanyl, in routine clinical practice it would be more satisfactory to use opioid premedication or "pretreat" the patients with fentanyl. It was satisfactory in that, being a rapidly acting drug, there was a quick response to alterations in the infusion rate. At this stage in the development of a new technique the use of a more slowly acting drug such as ketamine or midazolam would have been unwise.

Total i.v. anaesthesia necessitates the achievement and maintenance of drug concentrations sufficient to produce the desired response, but below those associated with undesirable side effects. Such may be obtained by the use of a single constant rate infusion, but it will take three to four times the elimination half-life before a constant minimal effective plasma concentration is achieved and, even with the shorter-acting agents, this will take a number of hours. Increasing the rate of delivery or the concentration of the infusion will increase the plasma concentration, but not the time taken to achieve a "steady-state" (Greenblatt and Koch-Weser, 1975). The use of a small loading dose followed by a single constant-rate infusion overcomes this problem to some extent. However, the plasma concentrations may decrease temporarily below therapeutic values and lead to a temporary lightening of narcosis. Increasing the size of the loading dose to avoid the decrease in plasma concentration increases the likelihood of early toxicity, while increasing the rate of infusion increases the likelihood of the side effects mentioned above.

These problems may be overcome by the use of multiple small bolus injections along with a constant-rate infusion, or by using, initially, a rapid constant-rate infusion and then decreasing this to a slower maintenance rate (Wagner, 1974). While these methods produce a more constant plasma concentration–time profile than infusion alone, they require interventions at strictly defined times after initiating therapy. Failure to carry these out at the appropriate times can lead to suboptimal conditions.

Our study shows that it is possible to achieve a constant plasma concentration of a drug using this simple method of delivery of an exponentially decreasing concentration of anaesthetic. If, with our dosage, patients are given a neuromuscular blocking drug and subjected to artificial ventilation, one would have no fear of recall during operation. However, with spontaneous breathing, methohexitone is not the drug of choice for this technique.

The logical extension of this study is the use of opioid premedication or the concomitant use of infusions of short acting opioids. Alfentanil would appear to be suitable for this purpose (Bowen and Hull, 1982; Ausems and Hug, 1983) and worthy of study in this field. This could also eliminate the need for nitrous oxide and it would improve the quality of anaesthesia with methohexitone.

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COMPARISON OF INFUSIONS OF ALFENTANIL OR PETHIDINE FOR SEDATION OF VENTILATED PATIENTS ON THE ITU

P. M. YATE, D. THOMAS, S. M. SHORT, P. S. SEBEL AND J. MORTON

SUMMARY

Sedation was studied in 30 patients requiring overnight ventilation in the intensive therapy unit (ITU). Patients received an infusion of either alfentanil or pethidine, supplemented with midazolam. The infusion rates were adjusted to provide optimal sedation as judged by a nurse, and measurements were made of quality of sedation, recovery and serum cortisol concentration. In addition, blood concentrations of alfentanil were measured to permit pharmacokinetic and pharmacodynamic analysis. Satisfactory sedation was achieved in both groups. The required infusion rate for alfentanil was between 0.4 and 0.5 $\mu g\ kg^{-1}\ min^{-1}$. Recovery was good in both groups, apart from one patient in the alfentanil group, in whom recovery was greatly prolonged and alfentanil pharmacokinetics were abnormal. A difference was found in the metabolic response to surgery between the two groups, the response in the alfentanil group being significantly less marked.

The ideal agent with which to sedate patients in the intensive care unit should provide cardiovascular stability, respiratory depression, reduction of intracranial pressure and analgesia. Ideally, it should have a pharmacokinetic profile which promotes its use by infusion. In addition, there should be minimal immunological or metabolic effects, a high therapeutic ratio and absence of active metabolites.

The withdrawal of Althesin, reports of cortisol suppression with etomidate (Lambert et al., 1983) and disordered pharmacokinetics with midazolam (Byatt et al., 1984), and a general dissatisfaction with some of the more traditional agents (Gast, Fisher and Sear, 1984) have necessitated a search for new agents in this field.

Alfentanil, a new short acting opioid, would appear to fulfil many of the above criteria. These include good cardiovascular stability even in high dose (Sebel, Bovill and van der Haven, 1982) and a short elimination half-life of approximately 90 min (Bovill et al., 1982) which has led to its successful use by infusion both during surgery (Ausems, Hug and de Lange, 1983) and to provide postoperative analgesia (Andrews et al., 1983; O'Connor, Escarpa and Prys-Roberts, 1983). A pilot study (Yate, Thomas and Sebel, 1984) suggested that alfentanil could be useful when given by infusion in the ITU.

The purpose of the present study was to investigate the suitability of alfentanil by infusion in a comparison with pethidine. Dose requirements, adequacy of sedation, quality of recovery, metabolic effects and pharmacokinetics have been assessed.

PATIENTS AND METHODS

Thirty patients requiring postoperative ventilation after open heart surgery were studied. All patients gave informed consent and the study had the approval of the local Ethics Committee. The patients were randomly allocated, using a computer-generated randomization code, to one of two groups: alfentanil (A) or pethidine (P). A standard anaesthetic technique was used: premedication was with lorazepam 2–4 mg by mouth 2 h before surgery and promethazine 25–50 mg plus

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P. M. YATE, M.B., B.S., F.F.A.R.C.S., S. M. SHORT, M.B., B.S., F.F.A.R.C.S., P. S. SEBEL, M.B., B.S., PH.D., F.F.A.R.C.S.I. (Anaesthetics Unit); D. THOMAS, M.B., B.S., F.F.A.R.C.S. (Department of Anaesthetics); J. MORTON, M.SC. (Department of Chemical Pathology); London Hospital Medical College, Whitechapel, London E1 1BB.

papaveretum 15–20 mg i.m. 1 h later. Anaesthesia was provided with thiopentone, nitrous oxide in oxygen, halothane, midazolam (up to 10 mg) and fentanyl (up to 1000 μg). After surgery the patients were transferred to the intensive therapy unit and artificial ventilation (to normocapnia) continued until 8.00 a.m. the next day. Once in the intensive care unit, patients were not sedated until they had awoken from the anaesthetic—defined as the time when they could open their eyes and move all four limbs to command.

Patients in group A received midazolam 2.5 mg and alfentanil 15 $\mu g\ kg^{-1}$ i.v. followed by alfentanil 0.4 $\mu g\ kg^{-1}\ min^{-1}$ by infusion. Patients in group P received midazolam 2.5 mg followed by an infusion of pethidine 10 $mg\ h^{-1}$. The injection of midazolam was given 3 min after the administration of the bolus of alfentanil, as earlier experience had shown that the simultaneous administration of alfentanil and midazolam could result in severe hypotension. The infusion rates in both groups were then adjusted by the ITU staff to provide optimal sedation. In addition, staff were given the option of incremental doses (alfentanil 15 $\mu g\ kg^{-1}$ or pethidine 10 mg) of opioid if the patient became unsettled, or of midazolam 2.5 mg i.v. if the patient was considered to be pain free and accepting IPPV, but too aware. After preliminary experience it was decided to give electively midazolam 2.5 mg to all the patients in the evening, to induce sleep.

The quality of sedation was assessed hourly by the nursing staff using a four point sedation score:
1 = Patient asleep or awake but needing no more analgesia.
2 = Mildly restless, but answers "no" when asked if more analgesia required.
3 = Mildly restless, answering "yes" to above.
4 = Restless, difficult to ventilate or in obvious pain.

As sedation was scored by a variety of nurses, an observer reliability study was conducted on similar patients using the method of Gelfand and Hartmann (1975).

The infusions were stopped at 8.00 a.m. the next day. Regular attempts were made to initiate satisfactory spontaneous ventilation (as judged by a ventilatory rate >12 b.p.m.). The trachea was extubated after approximately a further 15 min if the Pa_{CO_2} was less than 6.0 kPa. The hourly ventilatory rate and arterial $P\text{CO}_2$ were recorded for 6 h after the cessation of the infusion in the spontaneously breathing patients, as were the times to spontaneous ventilation and extubation, and the first demand for further analgesic. As it is the practice in this unit to give prophylactic analgesics before removal of the chest drain, all patients were given pre-mixed 50% nitrous oxide in oxygen to breathe during this procedure. The degree of drowsiness following the end of the infusion was assessed hourly for 6 h using an assessment scale:
1 = Asleep and unrousable.
2 = Asleep but rousable.
3 = Awake but drowsy.
4 = Wide awake and alert.
This assessment was performed by one person, a research nurse, who was unaware which sedative had been prescribed.

Blood was taken for the measurement of serum cortisol concentration at 17.00 h on the day before surgery, 17.00 h and 20.00 h in the ITU on the day of surgery (during the infusion) and at 17.00 h on the first day after operation. Samples to permit measurement of the concentration of alfentanil (group A) were taken before commencing the infusion of alfentanil, at 1 h, 6 h, 12 h, immediately before the cessation of the infusion, and then at 2, 5, 10, 15, 30, 60, 120, 360, 400, 600 and 960 min after the discontinuation of the infusion. Samples were frozen and assayed at a later date, cortisol by a standard radioimmunoassay (Amerlex) and alfentanil by gas chromatography (Woestenborghs, Michielsen and Heykants, 1981).

The distribution and elimination half-lives for alfentanil were calculated using the plasma concentrations obtained after stopping the infusion of alfentanil. These were fitted to single and bi-exponential curves by non-linear regression (BMDP3R A Statistical Package, copyright Regents of the University of California). The clearance of alfentanil was calculated from the area under the curve as measured by the trapezoid rule. The volume of distribution was calculated from clearance × elimination half-life/0.693. Statistical analyses were performed using analysis of variance, Student's *t* test, Mann–Whitney and Chi Square tests, where appropriate. Results were considered significant at $P < 0.05$ and are expressed as mean ± SEM.

RESULTS

Thirty patients were studied; one patient was excluded as a clinical decision was made not to ventilate the patient overnight. The demographic

TABLE I. *Details of patients studied (mean ± SEM)*

	Group A (alfentanil) (n = 14)	Group P (pethidine) (n = 15)
Age (yr)	58.3 ± 1.76	57.4 ± 1.65
Weight (kg)	68.0 ± 2.34	73.1 ± 3.87
Bypass time (min)	119 ± 11	115 ± 12
Fentanyl dose (µg)	817 ± 56	825 ± 35

data, surgical and anaesthetic details were similar between the two groups (table I). All patients had normal preoperative hepatic and renal function as determined by routine biochemical screening.

The mean durations of the infusion in both groups were not significantly different: 17.2 ± 0.56 (range 11.25–19.75) h in group A and 17.8 ± 0.45 (range 15–21.8) h in group P. The dose of midazolam 6.16 ± 2.6 mg in group P was larger, but not significantly so, than in group A, 4.28 ± 0.56 mg. The mean infusion rates of alfentanil and pethidine were 0.46 ± 0.028 µg kg^{-1} min^{-1} and 0.3 ± 0.02 mg kg^{-1} h^{-1}, respectively. The total dose of drug administered was 0.48 ± 0.036 mg kg^{-1} of alfentanil and 5.3 ± 0.43 mg kg^{-1} of pethidine. In group A, 22 extra incremental doses of alfentanil were given and the infusion rate had to be adjusted 14 times; in group P 10 incremental doses of pethidine were given and the rate had to be adjusted 56 times—significantly ($P < 0.05$) more often than in group A.

The mean infusion rates for the two groups are shown in figure 1. There was no significant increase in the infusion rate with time in either group; the initial increase in rate in the pethidine group, although not significant, possibly reflects an inadequate starting rate in some patients. Conversely, the mean plasma concentrations of alfentanil showed a significant increase ($P \le 0.05$) during the infusion of that drug.

There was no statistically significant difference in the sedation scores between the two groups (fig. 2). On only 2% of the hourly assessments was the sedation considered totally unsatisfactory, in both groups. No clear relationship between the plasma concentrations of alfentanil and the sedation score could be found. The reliability of the nurse assessment score was 90%.

The mean times to extubation, spontaneous ventilation and first demand for analgesia are shown in table II. In both groups 80% of patients were breathing spontaneously in 30 min and in 70% the trachea was extubated within 1 h of stopping the infusion. The prolonged recovery

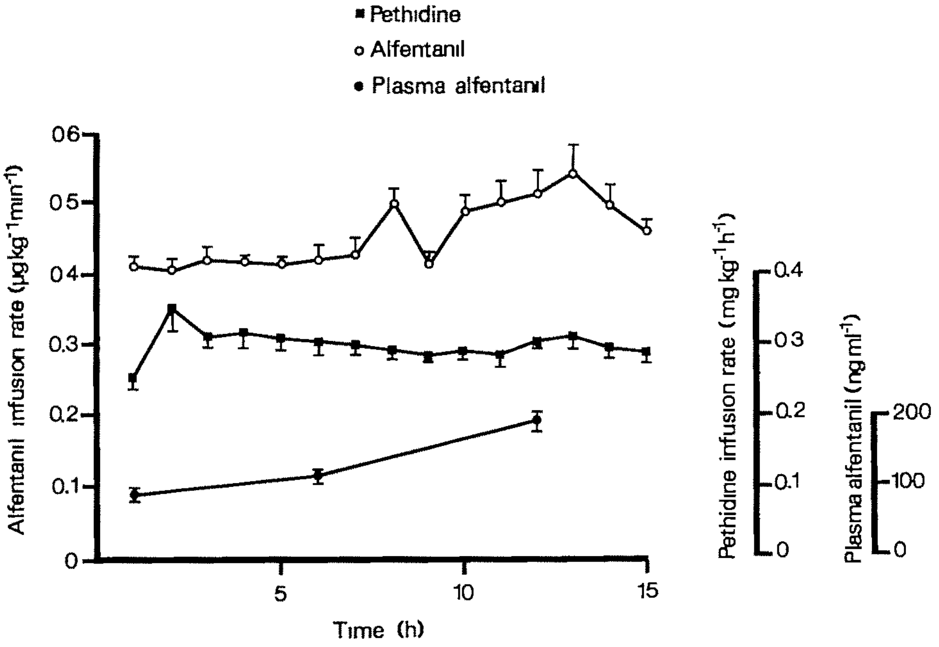

FIG. 1. Mean infusion rate of alfentanil and pethidine over the first 15 h of the infusion and plasma concentrations of alfentanil taken at 1, 6 and 12 h (mean ± SEM).

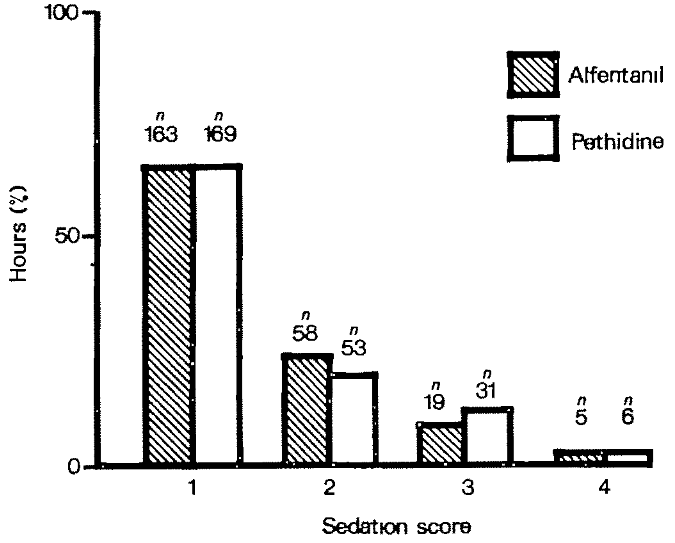

FIG. 2. Distribution of sedation scores expressed as a percentage of total number of hourly assessments at each score.

TABLE II. *Recovery times (median and range)*

	Group A (alfentanil)	Group P (pethidine)
Time end of infusion to spontaneous ventilation (min)	15.5 (5–230)	10 (1–60)
Time to extubation (min)	40 (25–231)	36 (1–110)
Time to first demand for analgesic (min)	180	210

times in group A were attributable to one patient (No. 15) and, if she is excluded, the mean times to spontaneous ventilation and extubation were, respectively, 16.7 ± 11.4 min and 51 ± 24 min in group A and 16.8 ± 5.2 min and 49.5 ± 7.8 min in group P. This patient behaved quite differently to the others in the group; extubation was not possible until 230 min after the cessation of the infusion and then only after naloxone 0.3 mg i.v. Respiratory rate and arterial $P\text{CO}_2$ were satisfactory for a further 420 min when she suddenly had a

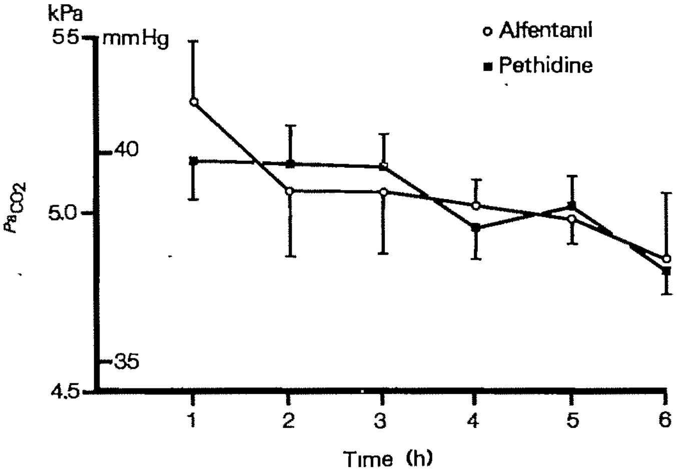

FIG. 3. Mean arterial (± SEM) $P\text{CO}_2$ for 6 h after cessation of the infusion in those patients breathing spontaneously.

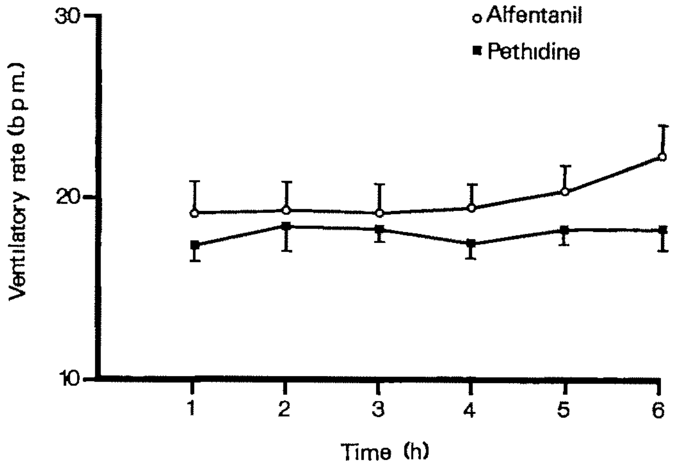

FIG. 4. Mean ventilatory rate (± SEM) for 6 h after cessation of the infusion in those patients breathing spontaneously.

respiratory arrest which was treated with a further naloxone 0.4 mg i.v. and i.m. Subsequently, she made a good recovery. Examination of the patient's records could not identify any special features apart from her general physical state, which was poor, and that she was one of only two patients in the trial to receive erythromycin.

There was a wide range in post-infusion demands for analgesia: two patients in group A and three in group P did not require any in the first 10 h after infusion.

The mean arterial $P\text{CO}_2$ and ventilatory rate in the first 6 h in the spontaneously breathing patients are shown in figures 3 and 4. There were no significant differences between the two groups. In addition, no difference was detected in the degree of postoperative drowsiness between the two groups (fig. 5); no patient was classified as unrousable at any time.

Cortisol concentration

These results are shown in figure 6. There were no significant differences between the groups in the preoperative cortisol values or in those

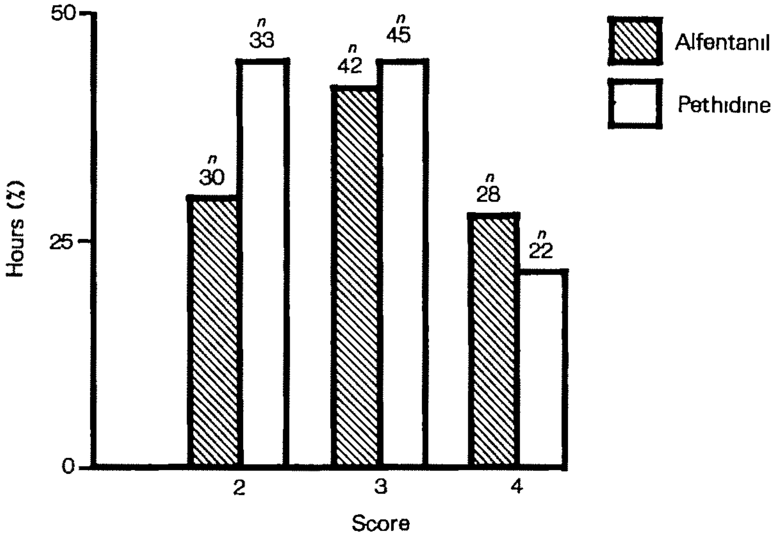

FIG. 5. Results of assessment scale of drowsiness in the post-infusion period. This is expressed as a percentage of the total number of hourly assessments at each score.

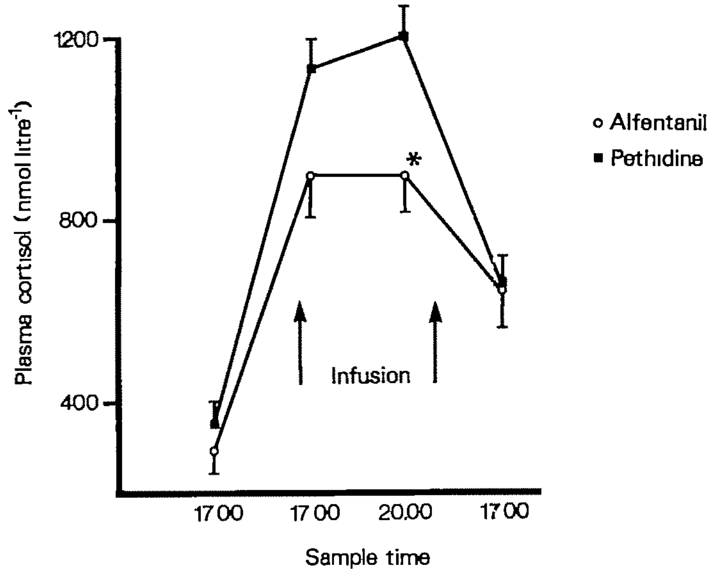

FIG. 6. Changes in plasma cortisol concentration (mean ± SEM) before, during and after the sedative infusions. *$P < 0.01$.

TABLE III. *Pharmacokinetic data of alfentanil infusions.* V_D = *Volume of distribution*

No.	Age (yr)	Weight (kg)	Sex	Distribution half-life (min)	Elimination half-life (min)	Clearance (ml kg^{-1} min^{-1})	V_D (litre kg^{-1})
1	48	65	M	51	298	3.14	1.3
2	45	65	M	3.7	48	4.26	0.29
3	59	70	M	10.3	108	3.44	0.54
4	53	70	F	40	90	2.78	0.36
5	57	69	M	19.2	180	2.34	0.6
6	65	71	M	63	238	1.68	0.58
7	59	50	F	11	253	3.32	1.2
8	58	71	M	3.6	85	2.48	0.3
9	55	75	M	4.3	134	1.83	0.36
10	68	74	M	2.9	169	2.16	0.53
11	67	72	M	1.15	234	1.86	0.63
12	55	85	M	123	115	2.7	0.45
Mean	57	70		27	162	2.66	0.59
SEM	±2	±2.3		±10.5	±22	±0.2	±0.09

obtained on the first day after operation. A marked response to the stress of surgery was seen in both groups. However, the mean cortisol concentrations at 20.00 h during the infusion were significantly lower in the patients receiving alfentanil ($P < 0.01$). The mean duration of the infusion at this time was similar in both groups.

Pharmacokinetics

Thirteen complete sets of plasma concentrations were collected, of which 12 could be fitted to single and bi-exponential curves. However, in all 12 a better fit, as judged by smaller residuals, was found with a bi-exponential decay. The derived pharmacokinetic variables are shown in table III. No curve could be fitted to the results from patient No. 15. The mean values of the 12 patients are plotted in figure 7; the results from patient 15 are shown separately. This patient can be seen to have kinetics markedly different from those of the other 12 patients, with a greatly prolonged half-life which was estimated at 720 min and a clearance,

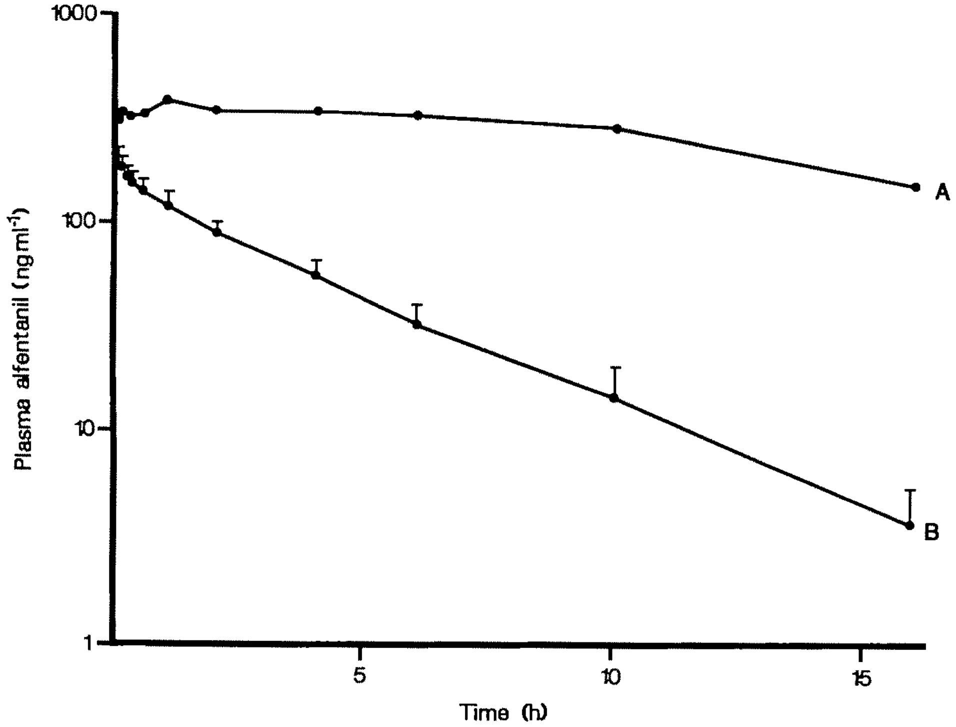

FIG. 7. Mean (± SEM) plasma decay curve in the 12 patients (B) and a separate plot of the post-infusion plasma concentrations in patient No. 15 (A).

estimated by extrapolating the plot, of 0.66 ml kg^{-1} min^{-1}.

DISCUSSION

Alfentanil has many theoretical advantages over other opioids in view of its high therapeutic ratio and previously published pharmacokinetic profile (Bovill et al., 1982). Concern has been expressed about pethidine on account of its potential cardiotoxicity (de Castro et al., 1979) and neurotoxicity related to nor-pethidine (Miller and Jick, 1978). Morphine has been reported to have unsatisfactory kinetics in renal failure (McQuay and Moore, 1984), a common problem in the ITU. There is little experience of the use of other opioids by infusion, most having a pharmacokinetic profile unsuited to prolonged administration by infusion.

We have compared an infusion of alfentanil with one of pethidine, both supplemented with a very small dose of midazolam. Pethidine was chosen for comparison on account of its regular use in this unit. Moreover, infusions of pethidine for postoperative analgesia have been extensively studied (Church, 1979; Stapleton, Austin and Mather, 1979). The group of patients chosen for this study, although not typical of the patients in a general ITU (40% of the patients in our ITU) provided a homogeneous group for study.

The design of this study was to use variable infusion rates to provide good sedation and rapid recovery. We were able to provide comparable sedation with both groups. However, it is suggested by the significant increase in the number of changes in rate with the pethidine group that the sedation was easier to achieve with alfentanil. The infusion rates of alfentanil required were in the range 0.4–0.5 µg kg$^{-}+^{1}$ min^{-1}—similar to those reported previously (Yate, Thomas and Sebel, 1984) with unsupplemented alfentanil, although supplemented with midazolam in the present study. Although the previous report suggested that alfentanil could be used as the sole agent, midazolam had to be added in the pethidine group for satisfactory sedation, and in an effort to maintain comparability between the groups midazolam was given to the alfentanil patients as well. The mean infusion rate of pethidine was comparable with that previously reported for postoperative pain relief in non-ventilated patients (Stapleton, Austin and Mather, 1979).

The plasma concentrations of alfentanil required during the infusion were in the region 150–200 ng ml^{-1}, a concentration the same as that required for maintenance during nitrous oxide-supplemented alfentanil for lower abdominal surgery (Ausems and Hug, 1983).

The results for recovery (apart from patient No. 15) were acceptable in terms of lack of sedation and adequacy of respiratory rate and Pa_{CO_2} and, in terms of PCO_2 and ventilatory rate, better than previously reported (Andrews et al., 1983) after a short infusion of alfentanil for postoperative analgesia. Although the post-infusion plasma concentrations obtained in this study have been associated with respiratory depression as measured by carbon dioxide response curves (O'Connor, Escarpa and Prys-Roberts, 1983), the mean plasma concentrations (excluding patient No. 15) of alfentanil after infusion had decreased to less than 150 ng ml^{-1} by 30 min, a figure previously quoted (Ausems and Hug, 1983) for satisfactory spontaneous ventilation, a finding supported by the clinical results in this study.

Although this was not primarily a pharmacokinetic study, any planned administration of a drug by infusion for a long period should take into account the known pharmacokinetics of the drug in that particular situation. Most of the previously published pharmacokinetic data of alfentanil have been obtained after a single i.v. dose in healthy volunteers (Bower and Hull, 1982) or young healthy patients undergoing surgery (McDonnell et al., 1982; Fragen et al., 1983).

In one small study with patients undergoing open heart surgery (Hug, de Lange and Burm, 1983) in which the kinetics were studied before and after cardiopulmonary bypass, a prolonged elimination half-life was found after the post-bypass dose, as a result of an increase in the volume of distribution. There are no reports of the pharmacokinetics of alfentanil after prolonged infusions in the intensive care unit. The results obtained in the 12 patients with an acceptable bi-exponential fit show plasma half-lives similar to those obtained by Hug, de Lange and Burm (1983) in cardiac surgical patients, when a large dose was given after surgery. In that study the prolonged elimination half-life was attributable to an increase in the volume of distribution. In our study the total volume of distribution was smaller (0.59 litre kg^{-1})—more like that seen in general surgical patients (Schuttler and Stoeckel, 1982), the prolonged elimination half-life of 162 min in our study being the result of the reduced rate of clearance, 2.66 ml kg^{-1} min^{-1}.

The possible advantages of alfentanil are clouded by the potentially serious problem encountered in patient No. 15. Assuming the respiratory arrest was the result of the termination of the effect of the first dose of naloxone, the long duration of action of naloxone is surprising, although a wide variation in the half-life of naloxone has been reported (Aitkenhead et al., 1984). The plasma concentrations measured in this patient showed a greatly reduced clearance, leading to a very prolonged half-life. The reasons for this are unclear; there was no biochemical evidence of hepatic dysfunction, which might be expected to reduce clearance. This patient was receiving erythromycin, a drug that has been reported to interfere with drug excretion (Green and Clement, 1983). However, another patient in the trial (No. 7) was also receiving erythromycin and she had a normal clearance of 3.32 ml kg^{-1} min^{-1}, although a rather prolonged elimination half-life (253 min). There have been other reports of prolonged elimination half-life of alfentanil as a result of a reduced clearance, although not of this order. Notably, McDonnell, Bartokowski and Kahn (1984) suggested that it may be caused by an abnormality of hepatic hydroxylation similar to that seen with debrisoquine and phenacetin—an abnormality found in approximately 10% of the population.

The introduction of any new drug to the ITU requires careful investigation of any metabolic effect. Previous studies of the metabolic effects of alfentanil have been confined to the effect of large doses administered before open-heart surgery. In one study (de Lange et al., 1983) alfentanil 42 µg kg^{-1} given before surgery caused marked suppression of the metabolic responses to surgery, similar to that seen with sufentanil and fentanyl. In another study which investigated the metabolic effects of the administration of fentanyl 50 µg kg^{-1} after surgical stimulus (Bent et al., 1984), it was suggested that, once established, the normal stress response could not be suppressed by opioids. In our study, a surprising finding was the marked difference between the two groups. The reason for this is unclear; it may be an effect, on a reduced scale, similar to that seen with alfentanil during cardiac surgery, or a reflection of better sedation produced by alfentanil. If alfentanil is to be used for prolonged infusions in the ITU, further investigations of the metabolic effect are required.

In conclusion, we have shown that alfentanil at an infusion rate of 0.4–0.5 $\mu g\ kg^{-1}\ min^{-1}$ or pethidine at a mean infusion rate of 0.3 $mg\ kg^{-1}\ h^{-1}$ can be used as the main agent for sedation of ventilated patients in the ITU, with good recovery in the majority.

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INFUSION OF VECURONIUM CONTROLLED BY A CLOSED-LOOP SYSTEM

J. W. DE VRIES, H. H. ROS AND L. H. D. J. BOOIJ

SUMMARY

Closed-loop control of neuromuscular blockade, using a semi-continuous infusion of vecuronium, is described. In 28 patients, the average neuromuscular transmission was between 13 and 17% of control. Requirements for vecuronium averaged 1.1 μg kg^{-1} min^{-1} (0.8–1.5 μg kg^{-1} min^{-1}), being in the same range as for repeated bolus injections. No side effects were observed. After the infusion was stopped recovery was rapid. Only three patients required induced reversal of blockade.

The pharmacodynamic behaviour of vecuronium makes it suitable not only for administration as a single or repeated bolus, but also as a continuous infusion. As with any neuromuscular blocking drug, however, the considerable interindividual variability in requirement, and possible interactions with other drugs, make monitoring desirable. By combining the monitoring of neuromuscular transmission and the infusion of an appropriate drug, neuromuscular blockade can be maintained using a closed-loop system.

Automatic control in such a system can be achieved in two ways: proportional control (that is, varying the speed of infusion) or on-off control (switching the infusion pump on or off, thus injecting in a semi-continuous way). The present study was undertaken to assess the feasibility of controlling neuromuscular blockade by means of a closed-loop system based on the semi-continuous infusion of vecuronium.

PATIENTS AND METHODS

Closed-loop control system

A prototype of an evoked compound electromyograph (Neuromuscular Transmission Monitor (NTM), Organon Teknika) (Crul, Booij and Robertson, 1983; Windsor, Sebel and Flynn, 1985) was used to stimulate an appropriate nerve, and to measure the compound EMG. The right ulnar nerve was stimulated via surface electrodes at the wrist using pulses of supramaximal intensity and of 0.15 ms duration at a rate of 0.1 Hz. The compound EMG of the hypothenar muscles was displayed on a pen recorder. The output signal of the NTM served as the input for an electronic device, developed in the Department of Medical Physics, which contained three elements (fig. 1). The passive element β served as an adaptor between the NTM and a comparator. The comparator had an adjustable reference voltage (preset value) with an adjustable hysteresis. The controller consisted of a solid state relay and syringe pump (Hospal K10). It was switched "on" when the input of the comparator exceeded value A and was switched "off" when it was lower than value B (fig. 2).

The syringe contained vecuronium 24 mg in saline 60 ml (0.4 mg ml^{-1}), and the rate of infusion was set at 3 μg kg^{-1} min^{-1}. For comparison with the electromyogram, the mechanomyogram (MMG) was also measured in six patients using a Statham UC3 force displacement transducer, and recorded on the pen recorder.

Patients

Twenty-eight patients (ASA status I or II), scheduled for urological, neurosurgical, gynaecological or general surgery, were included in the study. All were premedicated with nicomorphine, a narcotic analgesic, 7.5–10.0 mg and haloperidol 5 mg i.m. 1 h before surgery. After the induction of anaesthesia with thiopentone 4 mg kg^{-1} and fentanyl 2.5 μg kg^{-1} i.v., baseline measurements of neuromuscular function were obtained. Subsequently, a bolus of vecuronium 0.07 mg kg^{-1} i.v.

JAAP W. DE VRIES M.D., L. H. D. J. BOOIJ, M.D., PH.D. (Department of Anaesthesiology); H. H. ROS, PH.D. (Department of Medical Physics); Free University Amsterdam, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.

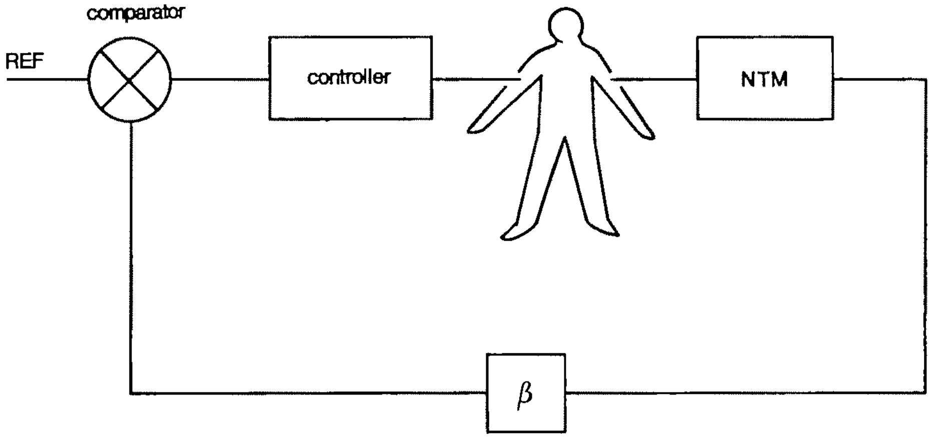

FIG. 1. Schematic diagram of the control system (for explanation see text).

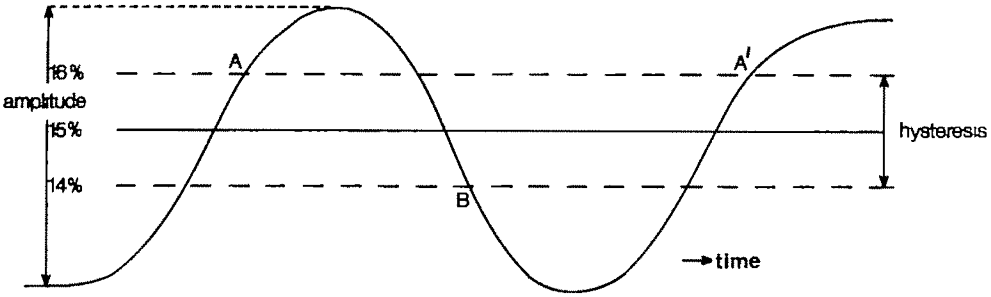

FIG. 2. Diagram showing oscillations around preset value (15%) attributable to control system. The difference between value "A" (16%) and "B" (14%) is called hysteresis (2%). Pump is on from A to B and off from B to A'.

was administered. The trachea was intubated when the twitch height had decreased to 30% of control or below. The closed-loop system was activated before neuromuscular blockade had recovered to 16% of control. Anaesthesia was maintained with 67% nitrous oxide in oxygen. Additional doses of fentanyl were given when required as judged by increases in heart rate and arterial pressure. Artificial ventilation was used throughout the procedure (end-tidal carbon dioxide concentrations between 4.5 and 5%). In neurosurgical patients, carbon dioxide concentrations were maintained between 3.5 and 4.0%. Approximately 20 min before the expected end of surgery the infusion of vecuronium was discontinued and blockade was allowed to recover spontaneously. Since there is spontaneous recovery during the "off-phase" in the "on–off" cycle, recovery time can be estimated from the slope of the curve (fig. 2).

RESULTS

After the bolus injection of vecuronium, twitch height decreased to less than 15% of control in all patients. After the closed-loop system was started, a depression of neuromuscular transmission was obtained which oscillated around the preset value—in general between 13 and 17% of control. This provided excellent operating conditions in all patients. A representative recording is shown in figure 3.

Using this technique, twitch heights of less than 10 or greater than 25% of control were not observed. On all occasions when the MMG was recorded simultaneously, the degree of relaxation measured with both methods was identical.

The duration of infusion varied between 45 min and 10 h. Even after 10 h of infusion, there was no sign of cumulation; spontaneous recovery was rapid and complete in 25 of the 28 patients at the

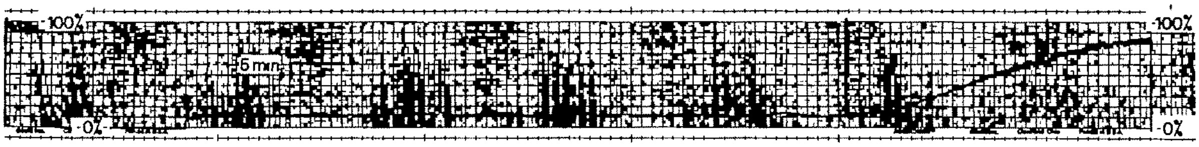

FIG. 3. Representative recording of the EMG signal. After a loading dose of vecuronium, 100% neuromuscular blockade was obtained. The infusion was started when blockade started to recover. Continuous 85% blockade was maintained. When the infusion was stopped spontaneous recovery was allowed. The occasional vertical deflections represent artefacts caused by cautery.

end of surgery. Although the average dose of vecuronium was 1.1 $\mu g\ kg^{-1}\ min^{-1}$, there were considerable variations in the requirement for vecuronium between patients, resulting in a range from 0.8 to 1.5 $\mu g\ kg^{-1}\ min^{-1}$. However, clinically stable blockade was easily obtained on all occasions. Once the infusion was stopped, recovery from neuromuscular blockade was rapid (average recovery time 11 min, range 5–22 min). At 70% recovery of twitch height, and at a train-of-four ratio of more than 50%, the patients were awakened. There were no clinical signs of residual neuromuscular blockade. In three of the 28 patients an antagonizing agent was required because surgery was terminated earlier than expected.

DISCUSSION

To date the most frequently used method of administering a non-depolarizing neuromuscular blocking drug is by bolus injection followed by additional increments, if required. When neuromuscular transmission is not monitored, this method may be satisfactory, especially when long-acting myoneural blockers are used. However, monitoring neuromuscular transmission allows better regulation of blockade because the administration of the neuromuscular blocker can be tuned to the individual patient. In addition, possible interactions with other drugs, such as antibiotics, can be detected. If the monitoring of blockade is performed in association with the continuous infusion of the drug, blockade can be controlled by means of a closed-loop system. Closed-loop control of neuromuscular blockade is not new: Ritchie, Spain and Reves (1984) developed a system using suxamethonium as the myoneural blocker. Brown and co-workers (1980) achieved the same using pancuronium and Cass and associates (1976) used gallamine, tubocurarine, alcuronium and pancuronium. In all of these studies the infusion was controlled by proportional regulation of the speed of infusion. Our method of choice was the "on–off" principle. The design of such a system is relatively simple in comparison with a proportional control system, and because of its pharmacodynamic profile, we regarded vecuronium as an ideal drug for use in such a system. Our system was tested in 28 patients during procedures which varied in duration from 45 min to 10 h. In all patients satisfactory neuromuscular blockade could be obtained easily. Oscillations in the degree of blockade were the result of the nature of the "on–off" system. The amplitudes of these oscillations depended on the hysteresis of the system, the "time-constant" of the drug, and the speed of infusion of the blocker (Gibson, 1963). A twitch height of less than 10% of control was regarded as excessive blockade because so many receptors are blocked that antagonism is difficult (Miller and Savarese, 1981). A twitch height greater than 30% of control provides insufficient surgical relaxation. In this study the oscillations never caused responses lower than 10% or higher than 25% of control twitch height and so did not interfere with the operative conditions. In 25 patients spontaneous recovery was rapid and complete. In only three patients was antagonism of residual neuromuscular blockade required—because surgery was terminated earlier than expected. Doses of vecuronium used (0.8–1.5 $\mu g\ kg^{-1}\ min^{-1}$) were in the same range as found by d'Hollander and colleagues (1982) for continuous infusion and, as in our experience, for repeated single bolus injections.

We conclude that the closed-loop control of neuromuscular blockade using the semi-continuous infusion of vecuronium is a safe and simple method with which to maintain a sufficient degree of blockade for intermediate to long procedures, and is especially useful if stable degrees of blockade are essential.

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SEDATION OF CHILDREN REQUIRING ARTIFICIAL VENTILATION USING AN INFUSION OF MIDAZOLAM

P. D. BOOKER, A. BEECHEY AND A. R. LLOYD-THOMAS

SUMMARY

The sedation of 50 children aged 6 months to 9 years who had undergone open heart surgery was studied. During artificial ventilation a midazolam infusion was used in conjunction with the administration of morphine (and tubocurarine). Sedation for patients breathing spontaneously with positive airway pressure was continued with midazolam alone. The duration of the midazolam infusion ($2–6\ \mu g\ kg^{-1}\ min^{-1}$) ranged from 12 to 197 h. Forty-seven of the children were sedated uneventfully; the remaining three children needed small doses of other sedative agents. In 10 of the children, blood samples were taken for serum midazolam assay and a short Synacthen test was performed. There was no clinical evidence of accumulation of midazolam, but midazolam concentrations were so variable that no conclusions could be drawn. All patients in whom they were measured (n = 10) had high basal cortisol concentrations, but displayed normal responses to Synacthen.

Long-term intubation of the trachea and intermittent positive pressure ventilation (IPPV) are among the commonest procedures carried out in the Intensive Care Unit (ICU). It is recognized that these can be subjectively distressing (Henschel, 1977; Shovelton, 1979; Green, 1980) and, consequently, sedation is usually required. Since the withdrawal of alphaxalone–alphadolone (Althesin, Glaxo), and the withdrawal of etomidate (Hypnomidate, Janssen) from use as sedatives in the ICU, the range of drugs available for this purpose is limited. Although the combination of an opioid with a benzodiazepine is used frequently, the durations of action of certain benzodiazepines, or their metabolites, can cause prolonged sedation (Editorial, 1984). In addition, some i.v. formulations are associated with a high incidence of thrombophlebitis (Kawar and Dundee, 1982). Moreover, if sedatives are prescribed and given on an intermittent "as required" basis to such patients, there is a danger that sedation may be inadequate (Miller-Jones, 1980).

Midazolam (Hypnovel, Roche) is an imidazolebenzodiazepine presented in aqueous solution. When administered as a single i.v. bolus, it has a plasma half-life of approximately 120 min (Smith, Eadie and O'Rourke-Brophy, 1981). Its two major psychoactive metabolites have even shorter half-lives and do not affect the overall duration of action of the drug (Clarke, 1982). Thrombophlebitis has not been a problem (Al-Khudairi, Whitwam and McCloy, 1982).

These properties suggested that it could be used to provide long-term sedation when given by i.v. infusion. Clinical experience with midazolam used in this way is limited, particularly in paediatric patients. This paper describes the use of an infusion of midazolam in 50 children who required sedation after open heart surgery.

PATIENTS AND METHODS

Fifty children, aged 6 months to 9 yr, were studied following elective cardiac surgery with cardiopulmonary bypass. The indications for surgery are

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P. D. BOOKER, M.B., F.F.A.R.C.S.; A. BEECHEY,* M.B., F.F.A.R.C.S.; A. R. LLOYD-THOMAS,** M.B., F.F.A.R.C.S.; Royal Liverpool Children's Hospital, Myrtle Street, Liverpool L7 7DG.

Present addresses:

*Department of Anaesthesia, Queens Medical Centre, Nottingham.

**Department of Anaesthesia, Saint Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

Correspondence to P.D.B.

TABLE I. *Indications for surgery*

Atrial septal defect	7
Ventricular septal defect	12
Complex ventricular septal defect	5
Transposition of the great vessels	9
Fallot's tetralogy	4
Aortic stenosis	4
Other valve defects	5
Other	4
Total	50

shown in table I. Patients who had been prescribed benzodiazepines in the previous 2 weeks or who had liver dysfunction other than as a result of cardiac failure were excluded.

The children were premedicated with trimeprazine 1.5 mg kg^{-1} by mouth 3 h before operation. Morphine 250 μg kg^{-1} i.m. and atropine 20 μg kg^{-1} i.m. were given 2 h later. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained subsequently with 50–66% nitrous oxide in oxygen. Morphine 250 μg kg^{-1} i.v. and tubocurarine 1 mg kg^{-1} i.v. were given before tracheal intubation was performed.

Patients were ventilated manually, using the Jackson–Rees modification of Ayre's T piece, at rates of 40–80 b.p.m., with sufficient fresh gas flow to produce mild hypocarbia (Pa_{CO_2} 4–4.7 kPa). Monitoring was instituted and venous access secured, after which a bolus of midazolam 200 μg kg^{-1} was given. Before surgery an infusion of midazolam was started at a rate of 2 μg kg^{-1} min^{-1}. Infusions were made up by diluting midazolam 3 mg kg^{-1} in 50 ml of 5% glucose in water. The infusion and bolus doses of midazolam were given through an i.v. cannula reserved exclusively for this purpose. On the institution of cardiopulmonary bypass, patients were cooled to 16–26 °C and another dose of tubocurarine 1 mg kg^{-1} was given. No more neuromuscular blocking agent was given until the patient arrived in the ICU. Rewarming to a temperature greater than 34 °C was achieved before bypass was discontinued. The infusion of midazolam was stopped at the time of insertion of the last skin suture.

The patients were then transferred to the ICU. Every 15 min thereafter, a standard stimulus—an orange stick drawn firmly along the sole of the foot—was applied. Sedative drugs were recommenced when the child had recovered sufficiently either to respond to this stimulus by withdrawing the whole leg or to show spontaneous eye-opening. An infusion of morphine was started at the rate of 0.15 μg kg^{-1} min^{-1} in those aged 6 months to 1 yr and at 0.3 μg kg^{-1} min^{-1} in those older than 1 yr. A bolus of midazolam 200 μg kg^{-1} was given and the infusion restarted, initially at 2 μg kg^{-1} min^{-1}. Tubocurarine 200 μg kg^{-1} was also given; subsequent doses of neuromuscular blocker were limited to a maximum of 100 μg kg^{-1} h^{-1}.

Quality of sedation was assessed by the nursing staff, who adjusted the rate of infusion as required. Patients were considered to be adequately sedated if they were asleep, tolerating ventilation and yet able to show a slight response to nursing procedures. If the patient was restless, the rate of the infusion of midazolam was increased in steps of 1 μg kg^{-1} min^{-1}, until satisfactory sedation was achieved. If there was no response to nursing procedures, the rate of infusion was decreased.

The duration of postoperative IPPV was determined by cardiovascular and respiratory variables. Pa_{CO_2} was maintained in the range 4–4.7 kPa and arterial and central venous pressures were monitored continuously. Urine output was recorded hourly.

When the patient's condition had improved such that weaning from IPPV was appropriate, the morphine and tubocurarine were stopped. Spontaneous respiration with continuous positive airway pressure (CPAP) was initiated when at least 4 h had elapsed after the administration of the last dose of neuromuscular blocking drug. The spontaneously breathing patient was then sedated with midazolam alone, until considered fit for extubation. The infusion of midazolam was stopped and extubation was performed when the patient was able to respond to verbal commands or was opening his eyes spontaneously. All assessments and decisions concerning weaning from IPPV and extubation were taken by one person (P.D.B.).

Blood samples for assay of midazolam concentrations were taken from 10 patients at the following times:

(1) After the induction of anaesthesia.
(2) At the time of last skin suture.
(3) When first awake in intensive care.
(4) 21.00 and 09.00 daily.
(5) On cessation of infusion of midazolam.
(6) When the patient awoke and was ready for extubation.

TABLE II. *Age and sex of the patients studied*

Age (yr)	Male	Female
< 1	6	5
< 2	8	7
2–5	6	7
5–10	4	7
Total	24	26

TABLE III. *Dose range of midazolam infusions*

Dose (μg kg^{-1} min^{-1})	Number
< 2	2
2–3	15
3–4	13
4–5	18
5–6	1
> 6	1
Total	50

Serum was separated, frozen and assayed (Roche Laboratories PLC).

A short Synacthen test was performed on these patients when they were stable, not requiring inotropic support and were sedated by midazolam alone. Within 48 h of their transfer to the paediatric ward, patients older than 6 yr were interviewed about any recollections of their stay in the intensive care unit.

RESULTS

In this series there were 24 boys and 26 girls whose ages ranged from 6 months to 9 yr (table II). In general, they weighed less than the median weight for their age. Distributions of age and weight were not markedly skewed.

The mean duration of the perioperative infusion of midazolam was 208 min (SD 68). After return to the ICU, the mean time to leg withdrawal was 132 min (SD 48). There was no correlation between this time and the duration of the perioperative infusion ($r = 0.06$).

Clinically adequate sedation was obtained in 47 patients (94%). The midazolam infusion rate ranged from 1.6 to 9.4 μg kg^{-1} min^{-1} (mean 3.8, SD 1.3). Only two patients required less than 2 μg kg^{-1} min^{-1} and one, more than 6 μg kg^{-1} min^{-1} (table III). The rate of infusion did not correlate with age ($r = 0.04$) or weight ($r = 0.09$).

TABLE IV. *Duration of midazolam infusion*

Duration (h)	Number
12–18	2
18–21	15
21–24	11
24–48	7
48–96	7
96–192	7
> 192	1
Total	50

The mean duration of the infusion of midazolam was 46.7 h (range 13–197, SD 42.9). Eight patients were sedated for longer than 96 h (table IV). At no time was any change in cardiovascular variables, or the need for cardiovascular support, attributed to the infusion of midazolam.

The mean time to recovery was 102 min (range 30–324, SD 54). Overall, 49 patients (98%) were judged to be ready for removal of the tracheal tube within 4 h of stopping the midazolam and in all the trachea was extubated uneventfully. The remaining patient required 324 min to recover sufficiently to permit extubation. In retrospect, his sedation had exceeded the requirements of the study.

The time from stopping the infusion to recovery and extubation did not correlate with age ($r = 0.16$) or weight ($r = 0.18$). However, in the one patient who was oversedated, recovery was slow.

Cortisol secretion was not inhibited by this sedative regimen. The mean plasma cortisol concentration was 947 nmol litre^{-1} (SD 126). Following the administration of Synacthen, the mean concentration increased to 1328 nmol litre^{-1} (SD 37).

One patient (2%) displayed an area of redness around the infusion site. No other local sequelae were seen. Of the 11 patients interviewed after discharge from the ICU, none could recall anything of the period of intubation, whether during the period of artificial ventilation or when breathing spontaneously.

DISCUSSION

In paediatric intensive care, it is essential that adequate sedation be provided, not only to aid compliance with artificial ventilation, but also to prevent awareness of a very frightening environment. Ideally, the sedative agent should have no cardiovascular or respiratory effects and its short elimination half-life would be by metabolic pathways independent of hepatic, renal and pulmonary function (Editorial, 1984).

With the recent loss of etomidate and Althesin, sedation in intensive care units is often provided by narcotic analgesics and benzodiazepines (Buchanan and Cane, 1978; Farina, Levati and Tognoni, 1981). Indeed, it was our usual practice to administer a long-acting benzodiazepine as part of the anaesthetic techniques described above. On return to the ICU, patients were sedated with morphine by infusion and intermittent doses of diazepam. Compliance with artificial ventilation was aided by the administration of tubocurarine. However, placing a limit of 100 $\mu g\ kg^{-1}\ h^{-1}$ on the dose of the neuromuscular blocking drug resulted in unacceptable quantities of diazepam being given. This caused a prolongation of the time to extubation—because the children were over-sedated. It also implies that our previous sedative regimen was inadequate.

Accordingly, we decided to continue to limit the prescription of neuromuscular blockers and to maintain existing infusion rates of morphine—which had been shown to produce satisfactory analgesia in children (Lynn, Opheim and Tyler, 1984). However, we decided to replace the long-acting benzodiazepine given during anaesthesia and the intermittent diazepam given in the intensive care unit by an infusion of midazolam.

Midazolam has been shown to be a safe and acceptable drug in paediatric practice when given as a single i.m. or i.v. injection either as premedication or as an induction agent (Cole, 1982; Sjovall et al., 1984; Gemperle and Rouge, 1981). However, there have been no reports of its use as an infusion in paediatric practice. Therefore, we performed a dose ranging pilot study in which, after a bolus dose of 200 $\mu g\ kg^{-1}$, an initial infusion rate of 2 $\mu g\ kg^{-1}\ min^{-1}$ was found to be optimal.

The formulation of midazolam, in particular its water solubility, has facilitated its use (Fragen, Gahl and Caldwell, 1978). The low incidence of thrombophlebitis in our series (2%) confirms its acceptable formulation, and is similar to that found in other series (Al-Khudairi, Whitwam and McCloy, 1982).

The infusion of midazolam provided smooth and reliable sedation, especially in the avoidance of sleep–wakening cycles often associated with the technique of "as required" sedation. Almost all patients (94%) were adequately sedated with infusion rates of between 2 and 6 $\mu g\ kg^{-1}\ min^{-1}$. The rapid onset of hypnotic activity (1–2 min) after i.v. injection, and the relatively brief half-life of midazolam (Smith, Eadie and O'Rourke-Brophy, 1981) allowed the nursing staff to titrate the rate of infusion against the response of the patient, thus producing adequate sedation. Bolus doses of 100 $\mu g\ kg^{-1}$, given by the nursing staff, were authorized if the child became very restless. However, these were not found necessary in this series of patients: simple adjustment of the infusion rate provided an adequately rapid response to control the minor restlessness that indicated inadequate sedation.

Midazolam concentrations measured in 10 patients were so variable as to prevent any conclusion being drawn. Variability of effect is a feature of sedation with benzodiazepines in general and has been noted when midazolam was used in other situations (Gamble et al., 1981). This may explain why three patients (6%) were sedated inadequately, despite an infusion rate of 6 $\mu g\ kg^{-1}\ min^{-1}$. The addition of trimeprazine 1 mg kg^{-1}, given every 6 h via a nasogastric tube, provided satisfactory control.

The design of this study did not permit statistical analysis of any of the cardiovascular effects of the infusion of midazolam. However, continuous monitoring and nursing of these patients, by staff trained to notice and act upon adverse cardiovascular changes, yield confidence that major adverse effects did not occur, and a clinical impression of cardiovascular stability was gained. Benzodiazepines are not regarded as possessing significant cardiovascular effects. The use of midazolam, compared with thiopentone, as an induction agent, has been associated with greater stability of arterial pressure in response to laryngoscopy and tracheal intubation (Boralessa, Senior and Whitwam, 1983).

Among our requirements for extubation are that the patient must have full protective laryngeal reflexes, respond to commands or spontaneously open the eyes. Thus we wait for most of the sedation to "wear off" before deciding to extubate the trachea. Forty-nine of 50 patients (98%) met these requirements within 4 h, despite infusions which lasted for 192 h in some patients. Reports of a prolongation of the action of midazolam in patients having major surgery and repeated administration of the drug (Byatt et al., 1984; Harper et al., 1985), have not been confirmed by our clinical findings. In these reports, the mode of administration of midazolam has not always been completely clear, but it is possible that the emphasis on constant patient assessment and the titration of the infusion rate against patient response prevented accumulation of the drug in this study. The prolongation of action, which appears to be more pronounced in adults, appears to be an alteration in the pharmacokinetics of the drug. Increases in the distribution half-life and the distribution volume have been reported (Byatt et al., 1984). A formal pharmacokinetic study has been undertaken and is reported in the following paper (Lloyd-Thomas and Booker, 1986).

Midazolam is converted to 1-hydroxy-methyl and 4-hydroxy metabolites (Clarke, 1982). The peak concentrations of these metabolites are seen 5–20 min after administration and at 1 h have decreased to 10% of peak values (Clarke, 1982). The short half-life of these potentially psychoactive metabolites was reflected in the rapid recovery time of the patients and is in contrast to clinical experience with repeated intermittent doses of diazepam.

Concern has been expressed recently over the ACTH-resistant suppression of cortisol synthesis by infusions of etomidate (Ledingham and Watt, 1983). This drug is thought to cause enzyme specific inhibition (Wagner et al., 1983). However, this is not known to occur with benzodiazepines. In patients receiving midazolam infusions, we found high cortisol concentrations. We conclude that this reflects the high degree of stress to which these children were subjected. Indeed, it is opposite to the depression of cortisol concentrations seen in adults sedated with oxazepam, which is thought to be common to all the benzodiazepines (Gram et al., 1984). Nevertheless, the patients studied demonstrated a normal response to Synacthen, albeit superimposed on increased basal concentrations of cortisol.

We suggest that an infusion of midazolam, when accompanied by an infusion of morphine, provides effective sedation which is superior to that provided by sedative regimens based upon intermittent administration.

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INFUSION OF MIDAZOLAM IN PAEDIATRIC PATIENTS AFTER CARDIAC SURGERY

A. R. LLOYD-THOMAS AND P. D. BOOKER

SUMMARY

Midazolam was given, by infusion, for the sedation of 10 children receiving intensive care after cardiac surgery. Plasma concentrations greater than 250 ng ml^{-1} were required for adequate sedation. Midazolam did not cumulate in eight of the 10 children, and these patients excreted the drug in a fashion similar to that by adults. However, midazolam did accumulate in two children, one with profound hepatic disturbance. In one of these patients recovery was slow following cessation of the infusion.

Critically ill patients who require intensive care are often in pain, fearful and anxious. Although analgesics can provide pain relief, and reassurance and communication can do much to relieve anxiety (Henschel, 1977; Shovelton, 1979), sedation is required frequently (Farina, Levati and Tognoni, 1981)—not only to provide anxiolysis, but also in the control of physically undesirable factors such as increases in intracranial pressure (Willatts, 1985). Clinicians have recently lost two useful hypnotic agents: Althesin (alphaxalone–alphadolone, Glaxo) was withdrawn by the manufacturers and etomidate (Hypnomidate, Jannsen) was shown to impair adrenocortical function when given by infusion over prolonged periods of time (Ledingham and Watt, 1983; Wagner et al., 1984).

With a more limited range of hypnotic agents available, a popular combination is that of an opioid and a benzodiazepine (Campos, Herraez and Marcos, 1980; Merriman, 1980; Miller-Jones and Williams, 1980; Farina, Levati and Tognoni, 1981; Reves, 1984). Diazepam has been used widely (Merriman, 1980), but the long elimination half-life and hypnotically active metabolite (n-desmethyldiazepam) may prolong recovery (Reves, 1984; Willatts, 1985).

Unlike diazepam, midazolam is water soluble and non-irritant to peripheral veins (Dundee et al., 1980; Kawar and Dundee, 1982). Its elimination half-life is 10 times less, and its total body clearance is some 20 times greater, than that of diazepam (Reves, 1984). The principal metabolite of midazolam is α-hydroxymidazolam, which is both hypnotically less active and has a shorter elimination half-life than the parent compound. Thus, when compared with diazepam, midazolam would be expected to have a shorter duration of action and, hence, be potentially a more useful agent with which to provide sedation i.v.

However, significant delays in awakening have been reported in some patients following sedation with midazolam (intermittent bolus and infusion) (Byatt, 1984; Byrne, Yeoman and Mace, 1984). In this unit, midazolam has been used widely in children requiring sedation following cardiac surgery (Booker, Beechey and Lloyd-Thomas, 1986). As a continuation of this study, the pharmacodynamics of midazolam when given by infusion have been investigated.

PATIENTS AND METHODS

The study was approved by the Hospital Ethical Committee and informed parental consent was obtained.

Selection of patients

Ten patients (two female) undergoing elective cardiac surgery requiring cardiopulmonary bypass were studied. Their ages ranged from 6 months to 8.75 yr. The defects requiring surgery are listed in table I. Patients who had received benzodiazepines in the preceeding 2 weeks or who

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A. R. LLOYD-THOMAS,* M.B., F.F.A.R.C.S.; P. D. BOOKER, M.B., F.F.A.R.C.S.; The Royal Liverpool Children's Hospital, Myrtle Street, Liverpool L7 7DG.

*Present address: The Department of Anaesthesia, Saint Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

Correspondence to A.R.L-T.

had clinical and biochemical evidence of hepatic dysfunction were excluded.

Anaesthesia

Patients older than 12 months of age received trimeprazine tartrate 1.5 mg kg^{-1} by mouth and morphine 0.25 mg kg^{-1} plus atropine 20 μg kg^{-1} i.m. given, respectively, 3 h and 1 h before surgery.

Anaesthesia was induced with thiopentone 4 mg kg^{-1} and morphine 0.25 mg kg^{-1} i.v. The trachea was intubated, following the administration of vecuronium 0.15 mg kg^{-1}, and anaesthesia maintained with 50% nitrous oxide in oxygen. Incremental doses of vecuronium 0.05 mg kg^{-1} were given as required, the last dose being administered just after the discontinuation of cardiopulmonary bypass. All patients were ventilated by hand, using the Jackson–Rees modification of Ayre's T piece, with sufficient gas flow to produce mild hypocarbia (Pa_{CO_2} 4.3–4.9 kPa).

Once appropriate monitoring had been established, a bolus of midazolam 0.2 mg kg^{-1} i.v. was given, and an infusion commenced at 2 μg kg^{-1} min^{-1}. This infusion was maintained throughout the operation and discontinued only at the time of the last skin suture. A dedicated peripheral line was used for the administration of midazolam.

Cardiopulmonary bypass

Core cooling to 16–26 °C was used in all patients. Re-warming to nasopharyngeal temperatures greater than 35 °C was achieved before the discontinuation of the bypass.

Sedation in the Intensive Care Unit

On arrival in the intensive care unit, and every 15 min thereafter, a standard stimulus (an orange stick drawn firmly along the sole of the foot) was applied. When the children had recovered sufficiently to respond by withdrawal of the leg, or to show spontaneous eye opening, they were re-sedated. A second bolus of midazolam 0.2 mg kg^{-1} i.v. was given and the infusion re-started at 2 μg kg^{-1} min^{-1}. An infusion of morphine was commenced at 0.33 μg kg^{-1} min^{-1}, a dose shown to produce satisfactory analgesia in children (Lynn, Opheim and Tyler, 1984). Vecuronium could be given if required, with the dose strictly limited to a maximum of 0.04 mg kg^{-1} h^{-1}.

The level of sedation was assessed by the nursing staff and the authors. Sedation was considered to be adequate when the children were asleep, tolerating artificial ventilation and yet able to respond slightly to nursing procedures such as endotracheal suction. If the patient was restless, the rate of infusion was increased in steps of 1 μg kg^{-1} min^{-1}, every 30 min until satisfactory sedation was achieved. If no response was elicted the rate of infusion was decreased.

Artificial ventilation

During intermittent positive pressure ventilation (IPPV) the Pa_{CO_2} was maintained in the range of 4.3–4.9 kPa. The duration of IPPV was determined by cardiovascular and respiratory variables. When these had improved such that weaning from IPPV was appropriate the morphine infusion was stopped. During intermittent mandatory ventilation (IMV) and spontaneous respiration with continuous positive airway pressure (CPAP), patients were sedated with midazolam alone. When the children were considered fit for extubation the midazolam infusion was stopped. Only when the patients were able to respond to

TABLE I. *Physical characteristics and lesions requiring surgery*

Patient No.	Age (months)	Sex	Weight (kg)	Defect requiring surgery
1	13	M	8.23	Aortic stenosis
2	6	M	6.15	Transposition of the great arteries
3	9	M	7.7	Transposition of the great arteries
4	60	M	16.6	Closure of ventricular septal defect
5	69	M	17.2	Mixed mitral valve disease
6	96	M	23	Closure of ventricular septal defect
7	20	F	14	Closure of ventricular septal defect
8	105	M	21.6	Atrio–ventricular canal defect
9	15	F	9	Closure of ventricular septal defect
10	13	M	6.4	Debanding of pulmonary artery and closure of ventricular septal defect

verbal commands or were opening their eyes spontaneously was extubation performed.

While the patient was on full ventilation, the arterial and central venous pressures were monitored continuously. In addition, during spontaneous breathing, the tidal volume, minute volume, respiratory rate and Pa_{CO_2} were measured. The urine output was recorded hourly.

Measurement of midazolam concentration

Blood samples for the assay of midazolam concentration were obtained at the following times:

(1) Base-line after induction.
(2) At the last skin suture.
(3) On awakening on the ICU.
(4) At 21.00 h and 09.00 h daily.
(5) On cessation of the midazolam infusion.
(6) On extubation.
(7) When possible during recovery.

Immediately following sampling, plasma was separated and frozen. Analysis was performed by the gas–liquid chromatography method of Heizmann and von Alten (1981) with electron capture detection.

Only limited patient sampling was possible once the children had awoken. Following cessation of the infusion, three samples were collected from five patients. From these three data points, in each patient, the approximate elimination half-life was calculated by least squares regression analysis of log drug concentrations against time.

RESULTS

Satisfactory sedation was achieved in all patients. In eight children the mean duration of infusion was 23.4 h (SEM 0.69 h). Two patients received longer infusions (table II), they also handled the drug abnormally and their results are presented later.

In the eight patients the mean duration of the perioperative infusion was 204 min (SEM 17), after which the mean plasma concentration of midazolam was 257 ng ml^{-1} (SEM 29.3). The mean time to awakening on the ICU following surgery was 114 min (SEM 12.5) during which the mean plasma midazolam concentration had decreased to 140.5 ng ml^{-1} (SEM 21.7) (table III, fig. 1).

After stable clinical sedation had been achieved with both midazolam and morphine, the mean plasma concentration of midazolam was 421 ng mg^{-1} (SEM 95.6). The mean infusion rate

TABLE II. *Duration of the midazolam infusions*

Patient No.	Duration of infusion (h)
1	24
2	21
3	23.5
4	26.25
5	68.5
6	113.5
7	23.25
8	25.5
9	21.5
10	22.45

TABLE III. *Duration and plasma concentration achieved at similar stages during the infusion of midazolam in eight children. Mean (± SEM).* *n = 7

Period	Duration (min)	Plasma midazolam concentration (ng ml^{-1})
Operative infusion*	204 (17)	257 (29.3)
Time to awakening after surgery	114 (12.5)	140 (21.7)
Duration of sedation with midazolam and morphine	1033 (46.9)	421 (95.6)
Duration of sedation with midazolam alone	246 (26.6)	530 (74.5)
Time to awakening and extubation in ICU	109 (12.1)	254 (51)

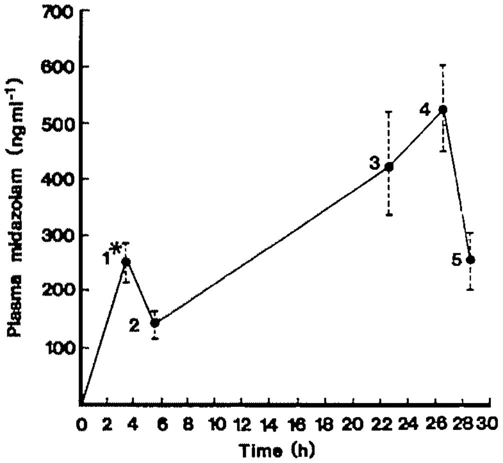

FIG. 1. Mean plasma concentrations of midazolam in eight patients at the following times: 1, at the last skin suture; 2, postoperative awakening in the ICU; 3, at steady clinical sedation the following day; 4, whilst sedated by midazolam alone and breathing on CPAP; 5, on awakening before extubation. Bars indicate ±SEM, * $n = 7$.

for the whole period of sedation was 3.1 $\mu g\ kg^{-1}\ min^{-1}$ (SEM 0.3), with a range of 2–5 $\mu g\ kg^{-1}\ min^{-1}$. While the patients were being sedated with midazolam and morphine, the mean midazolam infusion rate was 2.88 $\mu g\ kg^{-1}\ min^{-1}$ (SEM 0.3). However, when the patients were breathing spontaneously on CPAP, with midazolam as the only sedative drug, a significantly higher mean infusion rate (4.06 $\mu g\ kg^{-1}\ min^{-1}$ (SEM 0.3)) was required to maintain the same clinical level of sedation ($0.01 < P > 0.001$). During sedation with midazolam alone the mean plasma concentration increased to 530 $ng\ ml^{-1}$ (SEM 74.5). Plasma concentrations correlated closely with the mean infusion rate ($r = 0.87$, $0.05 < P 0.02$).

In the eight children the cardiovascular variables remained stable, during the administration of the bolus doses as well as the infusions of midazolam. During spontaneous respiration on CPAP the Pa_{CO_2}, minute volume, tidal volume and respiratory rate were within normal and expected values.

Following the discontinuation of the infusion of midazolam in the intensive care unit, the mean time to achieve a clinical state which would allow extubation was 109 min (SEM 12.1), during which the plasma concentration decreased to a mean of 254 $ng\ ml^{-1}$ (SEM 51). However, there was no correlation between the plasma concentration when the infusion was stopped and the time taken to recover ($r = -0.25$). There was no correlation between the plasma concentrations on awakening after surgery and those measured in relation to the second awakening (before extubation) ($r = 0.348$). In general, however, on both occasions, plasma concentrations on awakening were approximately one-half of those measured when the infusion was stopped (table IV).

From subsequent sampling it was possible to calculate the approximate elimination half-life in five patients. The mean elimination half-life was 4 h (range 2–8). Throughout the period of sedation the mean concentration of the metabolite alpha hydroxymidazolam was 26% (SEM 5%) of the mean midazolam concentration.

Much higher plasma concentrations were recorded in two children. In one (No. 6), hepatic impairment and renal failure occurred. In this child the mean rate of infusion (3.17 $\mu g\ kg^{-1}\ min^{-1}$) was not significantly higher than that in the other children. The increase in plasma concentration corresponded with increases in plasma liver enzyme and bilirubin concentrations (fig. 2). The

TABLE IV. *Plasma concentrations of midazolam present on awakening: A = following surgery; B = after prolonged sedation on the ICU*

Patient No.	Plasma concentration ($ng\ ml^{-1}$) A	B
1	117	246
2	74	246
3	114	233
4	265	523
5	198	3315
6	102	> 1200
7	188	78
8	91	396
9	122	129
10	53	177

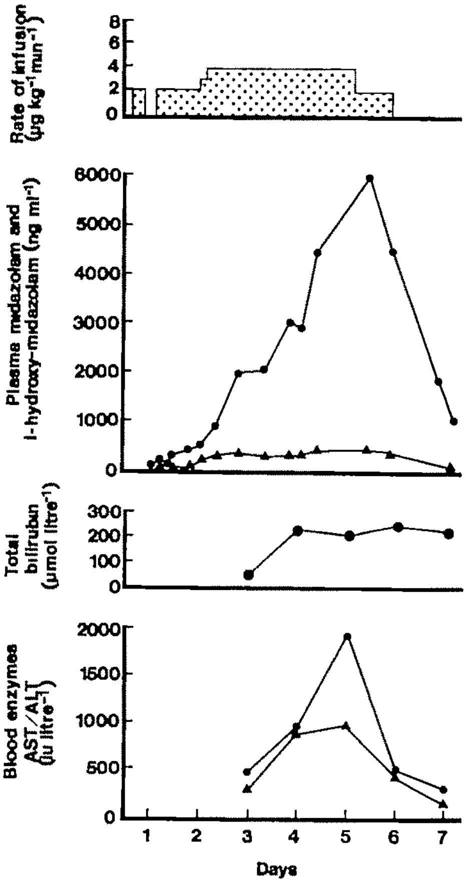

FIG. 2. Plasma concentrations of midazolam, 1-hydroxymidazolam, total bilirubin, aspartate transaminase and alanine transaminase as related to infusion rate in patient No. 6.

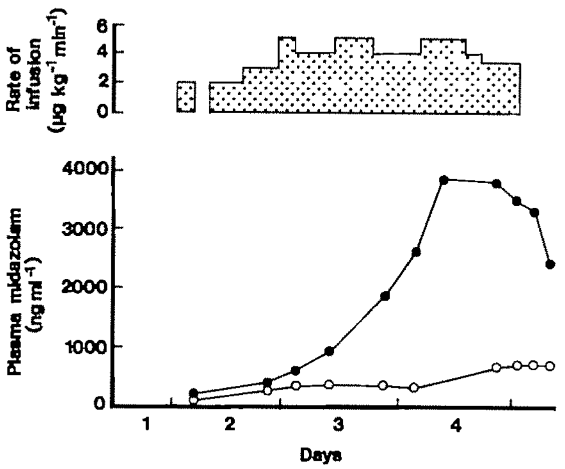

FIG. 3. Plasma concentrations of midazolam and 1-hydroxymidazolam as related to infusion rate in patient No. 5.

ratio of plasma α-hydroxymidazolam to midazolam was only 7.5% in this child, as compared with a mean of 26% in the other patients. Recovery was slow, following cessation of the midazolam infusion, taking 20 h and 30 min. The plasma concentration on awakening exceeded 1200 ng ml^{-1} (table IV, fig. 2). The second patient (No. 5) whose mean infusion rate (3.73 μg kg^{-1} min^{-1}) was also not significantly higher than the other children also had high plasma concentrations (fig. 3). The ratio, α-hydroxymidazolam to midazolam, of 17% was also reduced in comparison with the other patients. Recovery (200 min) was significantly longer than that of the other patients ($0.05 < P > 0.1$) and the plasma concentration of midazolam on awakening was 3315 ng ml^{-1}.

DISCUSSION

Reliable sedation with minimal side effects, and a rapid excretion which is independent of the body's metabolic pathways, is a goal unattained by any currently available drug.

In this investigation, reliable sedation was achieved in all patients with the infusion of morphine and midazolam. Periods of wakefulness, which are possible when hypnotic agents are prescribed on an "as required" basis (Miller-Jones and Williams, 1980) were avoided. During spontaneous respiration with CPAP, midazolam was the sole sedative agent and significantly higher infusion rates were required by all the children to achieve clinically equivalent sedation. This confirms the useful synergistic properties of morphine and midazolam.

Respiratory depression (depression of both the ventilatory response to carbon dioxide and the mouth occlusion pressure to carbon dioxide) of demonstrable CNS origin, has been described in patients given bolus doses of midazolam (Forster et al., 1980). However during weaning from IPPV none of the children showed any clinical evidence of respiratory depression. It has been suggested that "tolerance" to the respiratory depressant effects of midazolam occurs with repeated bolus dosage (Al-Khudhairi, Askitopoulou and Whitwam, 1982), a feature which could also occur in association with an infusion of the drug.

A reasonably good association has been reported between measured plasma midazolam concentrations, psychological performance and subjective sedation (Kanto and Allonen, 1982; Crevosier et al., 1983). Following a single i.v. dose of midazolam in adult volunteers under laboratory conditions, at concentrations of greater than 300 ng ml^{-1} the subjects were unrousable (Alloen, Zeigler and Klotz, 1981; Crevoisier et al., 1983). When combined with morphine the mean plasma concentration of midazolam, at steady clinical sedation in the children studied, was 421 ng ml^{-1}. This increased to 530 ng ml^{-1} during sedation with midazolam alone, when a higher rate of infusion was required. At these values the children were just slightly responsive to nursing procedures, yet able to tolerate IPPV. The range of plasma concentrations required to achieve clinically equivalent sedation in all the children studied was wide, but no child was adequately sedated with a plasma midazolam concentration of less than 250 ng ml^{-1}. Variability in the subjective assessment of the degree of sedation by the nursing staff could possibly have contributed to this wide range. However, only six out of a total of 30 alterations in the rate of infusion were made in the absence of an independent assessment by the authors, thus minimizing observer variation.

Within 165 min of stopping the infusion, eight children had recovered sufficiently to permit extubation of the trachea. The time to awakening following cessation of prolonged sedation was similar to that taken to awake following the shorter infusion during the perioperative period (table IV). In general, the plasma midazolam concentrations present at both times of awakening were approximately one-half those present when the infusion was stopped. However, in all but two children the plasma midazolam concentration on awakening before extubation was at least twice that present on awakening following surgery (table IV). The mean concentration on awakening before extubation was 254 ng ml^{-1}, which might be expected to cause marked sedation. Considerable cerebral tolerance to the depressant effects of the other benzodiazepines has been reported although, more usually, after several days' administration (Greenblatt and Shader, 1978; Dundee, 1979). The rapid development of cerebral "tolerance" could not account for these findings in our patients.

Prediction of the time to recovery after cessation of the infusion of midazolam was not possible from either the plasma drug concentrations or their half-lives. While in single-dose studies in healthy volunteers correlation between plasma concentration and clinical effect is reliable it appears, from this series, that this correlation is lost. Measured plasma concentrations of midazolam appeared to follow the trend of sedation in these children, but not in any precise manner.

Lack of cumulation with intermittent bolus administration has been reported in a group of adult patients following cardiac surgery (Lowry et al., 1985). If the clearance values in paediatric patients were similar to those previously measured in adults (Klotz and Reimann, 1984), plasma concentrations of between 200 and 850 ng ml^{-1} would be expected from the infusion rates used in these children. Eight of the 10 children fell within this range, thus implying a similar rate of clearance of midazolam. Midazolam accumulated in only two children.

The elimination half-life of midazolam in young healthy humans of normal body habitus is 1–4 h (Greenblatt et al., 1984). Of the five children in whom approximate elimination half-lives could be calculated, three were within the same range as the adults, while two were slightly prolonged at 6.5 and 8 h. In neither of the latter children was recovery prolonged.

The principal metabolite of midazolam is α-hydroxymidazolam (Reves et al., 1985). In this series the ratio of drug to metabolite (26%) was similar to that found in healthy adult volunteers (Vree, 1982). This provides further evidence that these children handled midazolam in a normal fashion.

However, in two children midazolam appeared to accumulate. In the first patient a poor cardiac output following surgery with associated splanchnic hypoperfusion was responsible for both the hepatic and renal injury. As a result the hepatic metabolism of midazolam was impaired and accumulation occurred (fig. 3). A low ratio of α-hydroxymidazolam to midazolam (7.5%) supports the impression of failure of metabolism. Recovery following cessation of the midazolam infusion was slow. In the second child there was no clinical or laboratory evidence of hepatic disturbance, yet midazolam appeared to accumulate. His recovery, although significantly longer than the other children, was not unacceptably prolonged.

Both of these children showed considerable "tolerance" to the sedative effect of midazolam, in that they awoke, after prolonged sedation, at considerably higher plasma concentrations than on their initial admission to the intensive care unit. This was especially evident in the second child who took only 200 min to awake (plasma concentration 3315 ng ml^{-1}). This "tolerance" may have considerably shortened the time of recovery of both children.

In conclusion, this study confirms the clinical impression of a previous report (Booker, Beechey and Lloyd-Thomas, 1986), that midazolam is a useful drug for the sedation of children receiving intensive care. It appears that the majority of the children investigated by this study handled midazolam in a manner similar to adults. However, caution should be exercised in critically ill patients in whom hepatic function may be impaired.

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ISOFLURANE DOES NOT REDUCE AORTIC PEAK FLOW VELOCITY IN CHILDREN

T. M. GALLAGHER, M. D. SHIELDS AND G. W. BLACK

SUMMARY

Haemodynamic effects of 1 MAC halothane, enflurane and isoflurane were studied in 15 healthy children using pulsed Doppler echo cardiography. Heart rate was significantly increased with isoflurane, but not with the other two agents. All three caused comparable decreases in arterial pressure. Cardiac output was increased with isoflurane, but remained unchanged with halothane and enflurane. Aortic peak flow velocity, a sensitive index of myocardial contractility, was decreased with halothane and enflurane, but not with isoflurane. These findings indicate that isoflurane causes less myocardial depression than halothane or enflurane in children.

Inhalation agents form the basis of the vast majority of anaesthetics given to children. Halothane is currently the most popular but enflurane and, more recently, isoflurane are being used with increasing frequency. Nicodemus and colleagues (1969) have suggested that children may be particularly susceptible to the cardiovascular depressant effects of volatile anaesthetics, but haemodynamic studies in children have been limited by the invasive nature of the available techniques. However, with the development of pulsed Doppler echocardiography, which is a safe, reliable and non-invasive technique, such investigations are now feasible (Alverson et al., 1982). The present study was undertaken to evaluate the haemodynamic effects of halothane, enflurane and isoflurane in children, using this method.

PATIENTS AND METHODS

The technique of pulsed Doppler echocardiography enables two-dimensional imaging and recording of blood flow velocity to be carried out simultaneously. Blood flow velocity is related to the measured Doppler frequency shift in accordance with the Doppler equation:

$$\bar{V} = \frac{\Delta fc}{2F \operatorname{Cos} \sigma}$$

where $\bar{V}$ = mean velocity; Δf = frequency shift; c = speed of sound in tissue; σ = angle of incidence of the ultrasonic beam. In the case of pulsed Doppler echocardiographic measurement of cardiac output, the velocity of blood flow in the ascending aorta is measured. Cardiac output is determined in accordance with the principles of fluid dynamics of pulsatile flow (Caro et al., 1978), flow through a cylinder being equal to the product of mean velocity of flow and the cross sectional area (c.s.a.) through which it passes. Thus cardiac output is equal to the product of the mean velocity of flow in the ascending aorta and the cross sectional area of the aorta. An ATL MARK 600 Duplex scanner was used and ultrasound was transmitted and received by a transducer placed in the suprasternal notch. The beam of ultrasound was directed at the ascending aorta and its position delineated by the cursor line with 2-dimensional imaging (fig. 1). Frequency shift signals from red blood cells undergo spectral analysis and the final outline shown on the oscilloscope represents velocity of blood flow in the ascending aorta in m s^{-1} (fig. 1).

The diameter of the aorta was obtained from the two-dimensional image and the c.s.a. of aorta estimated: $(\pi D^2)/4$. Mean velocity was determined by measuring the area between the curve and the zero velocity line and dividing by the distance along the x axis. Measurements were carried out on a Kontron Cardio 80 digitizing board, the mean

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THERESA M. GALLAGHER, M.D., M.R.C.P.I., F.F.A.R.C.S.I.; M. D. SHIELDS, M.B., M.R.C.P.; G. W. BLACK, M.D., F.R.C.P.I., F.F.A.R.C.S.; The Royal Belfast Hospital for Sick Children, Belfast, BT12 6BE.

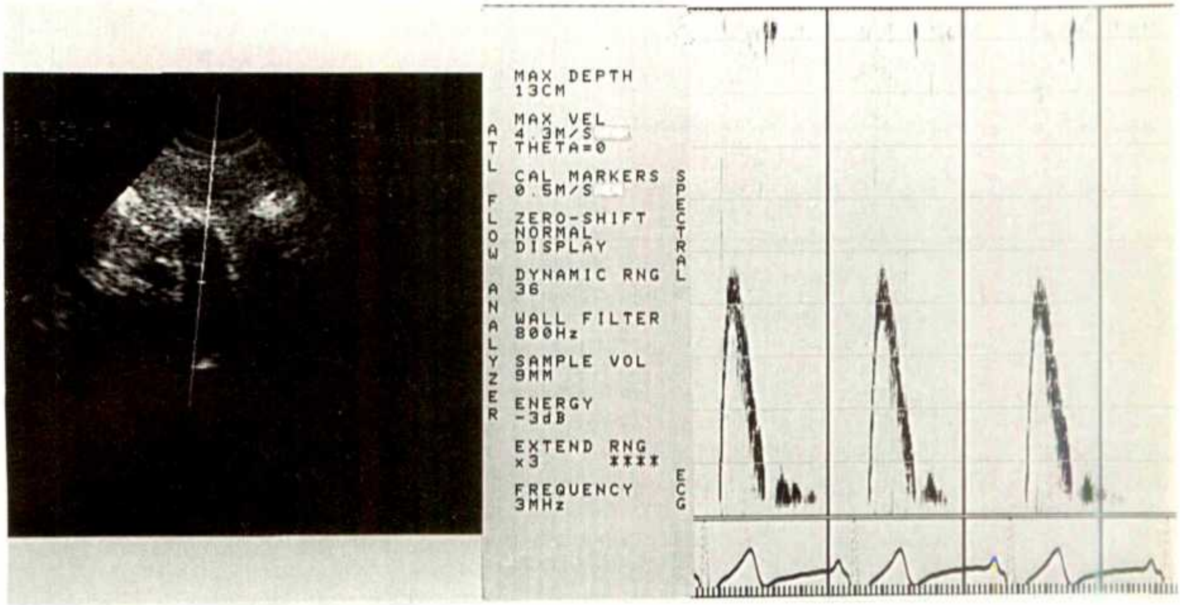

Fig. 1. Two-dimensional image of ascending aorta and typical tracing of aortic blood flow velocity ($m\ s^{-1}$).

velocity of five beats being averaged to eliminate the effects of respiration or rhythm changes. Stroke volume was derived by dividing cardiac output by heart rate. Control measurements were made when the children had become accustomed to the technique. In order to eliminate bias, calculations were made without the operator knowing which anaesthetic was being administered. Heart rate and rhythm were monitored continuously with the electrocardiogram, indirect arterial pressure with a Dinamap 845 oscillometer, temperature with an oesophageal thermistor probe and end-tidal carbon dioxide and anaesthetic concentrations with Datex infra-red analysers (Normocap and Normac).

Approval of the Research Ethical Committee and parental consent were obtained for the study. Fifteen healthy (ASA I) children were given halothane, enflurane or isoflurane on the basis of computer-generated random numbers. The children receiving the different anaesthetics were of comparable age and weight (table I). Control data were obtained with the child awake and after 30 min of 1 MAC anaesthesia. All measurements were made before surgery. Pre-anaesthetic medication was omitted, anaesthesia was induced with sodium thiopentone 5 mg kg^{-1}, neuromuscular blockade with suxamethonium 1 mg kg^{-1} and the trachea was intubated with a Portex gas sampling tracheal tube. When spontaneous breathing had returned, the volatile agent under study was administered in 100% oxygen using a Bain breathing system and the inspired concentration adjusted to maintain an alveolar concentration of 1 MAC for 30 min. The MAC values for the age groups studied were 0.9% halothane (Gregory, Eger and Munson, 1969), 1.8% enflurane and 1.5% isoflurane (Cameron, Robinson and Gregory, 1984). The data were analysed using the "Statistical Package For Social Sciences" (Nie et al., 1975). The effects of each agent were analysed with a paired t test and the differences between agents using the Neumann–Keuls test. Analyses were based on percentage alterations from control values.

TABLE I. *Physical characteristics of children (mean values ± SD)*

	Halothane	Enflurane	Isoflurane
Age (yr)	7.8±3.1	7.4±1.9	7.2±2.4
Weight (kg)	25.6±8.8	24.0±6.0	23.4±8.6

RESULTS

Heart rate was significantly increased with isoflurane ($P < 0.05$), but there was little alteration with either enflurane or halothane (table II, fig. 2). Systolic, diastolic and mean arterial pressures

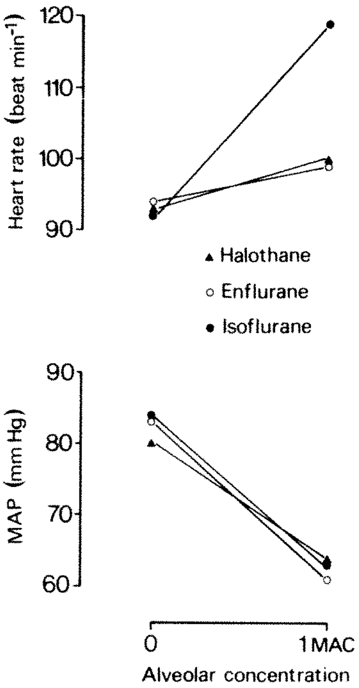

Fig. 2. Changes in heart rate and mean arterial pressure with halothane, enflurane and isoflurane.

were significantly decreased by all three agents, the reductions being largely comparable (tables II and III; fig. 2). Stroke volume was not significantly altered by any of the three agents (table IV). Cardiac output was increased significantly with isoflurane ($P < 0.05$), but remained unchanged with halothane and enflurane (table IV). Aortic peak flow velocity was significantly decreased with halothane ($P < 0.001$) and with enflurane ($P < 0.01$) (table V, figs 3 and 4) and, although it tended to increase with isoflurane, the increases were not significant. End-tidal carbon dioxide concentrations were comparable in all three groups at 30 min (6.4% halothane, 6.7% enflurane and 6.7% isoflurane).

Table II. *Effects of halothane, enflurane and isoflurane on heart rate (HR) and mean arterial pressure (MAP) (mean values ± SD). *P < 0.01; **P < 0.001*

	HR (beat min⁻¹)		MAP (mm Hg)	
	Control	1 MAC	Control	1 MAC
Halothane	92.6 ±24.3	99.8 ±27.0	79.6 ±2.6	64.0** ±6.0
Enflurane	93.8 ±23.6	98.8 ±21.4	83.3 ±7.2	61.2* ±4.2
Isoflurane	92.4 ±12.9	119.4* ±10.5	84.0 ±7.5	63.4* ±7.4

Table III. *Effects of halothane, enflurane and isoflurane on systolic and diastolic arterial pressures (mean values ± SD). *P < 0.05; **P < 0.001*

	Systolic pressure (mm Hg)		Diastolic pressure (mm Hg)	
	Control	1 MAC	Control	1 MAC
Halothane	119±13.5	104±12**	68±6.4	41±4.0*
Enflurane	122±9.5	101±3.5*	65±7.7	40±3.5**
Isoflurane	115±5.4	97±4*	62±5.6	45±8.7**

Table IV. *Effects of halothane, enflurane and isoflurane on cardiac output and stroke volume (mean values ± SD). *P < 0.05*

	Cardiac output (litre min⁻¹)		Stroke volume (ml)	
	Control	1 MAC	Control	1 MAC
Halothane	5.2 ±1.2	5.0 ±0.8	57.9 ±13.1	54.0 ±20.1
Enflurane	5.5 ±1.6	5.6 ±1.46	61.0 ±19.27	57.9 ±25.7
Isoflurane	4.75 ±0.98	5.9* ±1.76	54.0 ±19.4	48.8 ±14.8

Table V. *Effects of halothane, enflurane and isoflurane on aortic peak flow velocity (m s⁻¹) (mean values ± SD). *P < 0.01; **P < 0.001*

	Halothane	Enflurane	Isoflurane
Control	1.38 ±0.17	1.27 ±0.20	1.25 ±0.29
1 MAC	1.17** ±0.17	1.08* ±0.22	1.41 ±0.47

DISCUSSION

The main finding of this study is that low concentrations of halothane and enflurane, but not of isoflurane, decreased aortic peak flow velocity in children. Rushmer (1966) has suggested that aortic peak flow velocity is a sensitive index of myocardial contractility. It reflects the magnitude of the impulse generated by the contracting left ventricle during the initial stage of ejection (Rushmer, 1964) and is particularly sensitive to

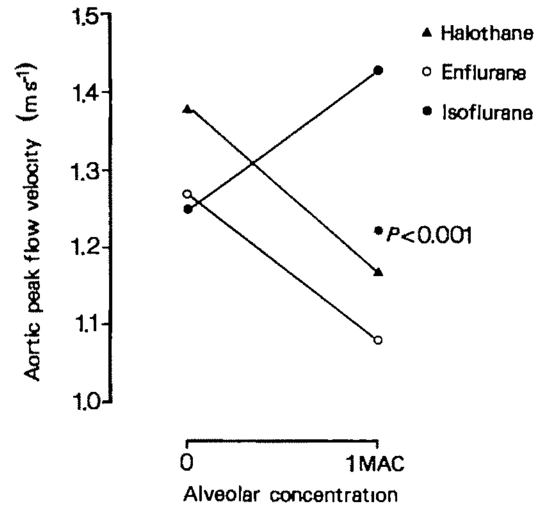

Fig. 3. The effects of halothane, enflurane, and isoflurane on aortic peak flow velocity.

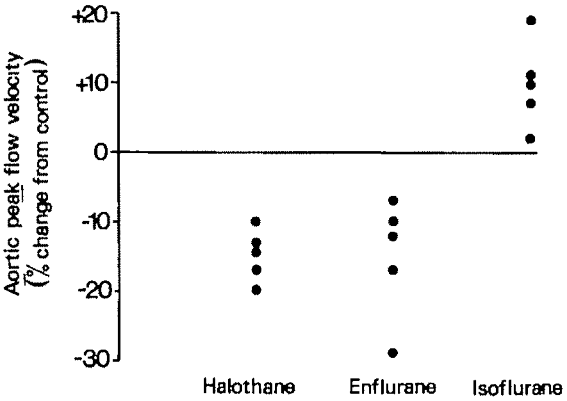

Fig. 4. Percentage alterations in aortic peak flow velocity.

changes in the inotropic state of the myocardium (Nutter, Nobel and Hurst, 1971). Thus it may be concluded that 1 MAC isoflurane causes less myocardial depression than 1 MAC halothane or enflurane. Comparable findings have been reported in adults by Stevens and his colleagues (1971) using the technique of ballistocardiography, which also measures the initial ventricular impulse. Recent investigations in children using M mode echocardiography provide further evidence that low concentrations of isoflurane do not adversely affect left ventricular function (McNeill, Lerman and Gregory, 1984; Neal et al., 1984).

It has been suggested that the difference in myocardial contractility between isoflurane and the other two anaesthetics may be caused by increased beta sympathomimetic activity (Stevens, Cromwell and Halsey, 1971; Balasaraswathi et al., 1982). It seems reasonable to assume that this may account for the increases in heart rate, cardiac output and aortic peak flow velocity found in the present study. Also, Hirshleifer and his colleagues (1975) have shown that acute increases in heart rate *per se* may augment myocardial contractility. All three agents produced comparable reductions in systolic, diastolic and mean arterial pressures. It is generally accepted that the hypotensive effects of halothane and enflurane are mainly caused by a decrease in cardiac output, while isoflurane causes substantial reductions in systematic vascular resistance (Jones, 1984). In the present investigation, only low alveolar vapour concentrations were studied and this may explain why neither halothane nor enflurane reduced cardiac output. Also, it is known that measurements of cardiac output based on pulsed Doppler echocardiography may be overestimated (Ihlen, Amlie and Dale, 1984), a common source of error being the measurement of aortic diameter and the calculation of aortic c.s.a. Although cardiac output determinations using pulsed Doppler echocardiography have been found to correlate favourably with those obtained by invasive methods (Darsee et al., 1980; Huntsman et al., 1983), it has been suggested that the technique may be more useful for comparing relative rather than absolute changes in cardiac output (Schuster et al., 1985).

Although it has been shown that spontaneous respiration may influence the cardiovascular effects of volatile anaesthetics (Cullen and Eger, 1974), only moderate increases in end-tidal carbon dioxide concentration were noted in the present study. Horan and colleagues (1977a, b) have reported that, in animal studies, minimum equipotent concentrations of halothane, enflurane and isoflurane have broadly comparable effects on conventional cardiovascular variables including arterial pressure, heart rate and cardiac output. However, they found that differences between the three agents became apparent when more sophisticated indices of myocardial contractility were studied.

Increases in heart rate were observed in children receiving isoflurane, a finding which has been reported in adults (Shimosato et al., 1982; Cahalan et al., 1983). This may be caused by increased sympathomimetic activity (Stevens, Cromwell and Halsey, 1971) and by preservation of baroreceptor responsiveness (Kotrly et al., 1984). Increases in heart rate may be associated with greater myocardial oxygen consumption (Braunwald, 1971). Although this may be of critical importance in the adult, especially in the presence of ischaemic heart disease, it is unlikely to be of clinical significance in the normal healthy child in whom increases in heart rate are well tolerated (Wetzel and Rodgers, 1981). It has been suggested (Brandom, Brandom and Cook, 1983; Boudreaux, Schieber and Cook, 1984) that the rapid body uptake of halothane may result in the development of high myocardial concentrations. This may account for the greater incidence of bradycardia, hypotension and cardiac arrest reported in children (Diaz and Lockhart, 1979). It is of interest that, although the uptake of isoflurane is more rapid in children than that of enflurane or halothane (Gallagher and Black, 1985), the findings of the present study indicate that it causes less myocardial depression than the other two agents. This suggests that, in children, there is a greater margin of safety with isoflurane than with other volatile anaesthetics.

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RESPIRATORY EFFECTS OF NITROUS OXIDE DURING ISOFLURANE ANAESTHESIA IN CHILDREN

I. MURAT, J. P. SAINT-MAURICE, L. BEYDON AND K. MACGEE

SUMMARY

Respiratory effects of nitrous oxide and isoflurane were studied in 13 children (mean age 45.6 ± 19.3 months, mean weight 14.9 ± 4.8 kg) during surgery under continuous extradural anaesthesia. Three different anaesthetic states were studied: (1) isoflurane 0.5 MAC in oxygen (27 study periods), (2) isoflurane 0.5 MAC with 50% nitrous oxide (32), (3) isoflurane 1 MAC in oxygen (25). End-tidal carbon dioxide ($P_{E'CO_2}$) and isoflurane, respiratory indices (tidal volume, V_T; minute ventilation, $\dot{V}_E$; mean inspiratory flow, $\dot{V}_I$; respiratory frequency f, effective inspiratory timing T_I/T^{tot} were measured. The addition of nitrous oxide (comparison of respiratory variables obtained in 25 successive periods at (1) and (2)) produced a significant increase in $P_{E'CO_2}$, significant decreases in V_T, $\dot{V}_E$ and $\dot{V}_I$, a significant increase in f. The increase in alveolar concentration of isoflurane ((1) compared with (3) in 25 successive periods) was associated with a significant increase in $P_{E'CO_2}$, significant decreases in V_T, $\dot{V}_E$, $\dot{V}_I$ and a significant increase in f. The equipotent anaesthetic states (2) and (3) were compared in 21 successive periods. In children, the net result of substituting nitrous oxide for an equal MAC fraction of isoflurane was to produce a smaller decrease in V_T responsible for a smaller decrease in $\dot{V}_E$ without significant change in respiratory rate.

Like all halogenated anaesthetic agents, isoflurane depresses respiration (Fourcade et al., 1971). However, the effect does not appear to be much greater than that of halothane, which is currently used widely in clinical practice (Nunn, 1985). When compared with halothane, isoflurane produces an identical decrease in tidal volume (V_T), but a greater decrease in minute ventilation ($\dot{V}_E$) because the increase in respiratory rate is less than with halothane (Fourcade et al., 1971). The substitution of 70% nitrous oxide for an equal MAC fraction of isoflurane seems to contribute, in adult patients, to decreasing this depressant effect on alveolar ventilation by increasing respiratory frequency (Eger et al., 1972).

In children aged between 1 and 6 yr, respiratory rate at rest is greater than in the adult (Taussig, Harris and Lebowitz, 1977). During nitrous oxide–halothane anaesthesia, the increase in respiratory frequency is related to the inspiratory concentration of halothane (Murat et al., 1985). During nitrous oxide–isoflurane anaesthesia in the same age group of children, however, the change in respiratory frequency was not related to the increase in the inspired concentration of isoflurane. An increase in respiratory frequency was found in association with light anaesthesia, but no further changes occurred as anaesthesia was deepened (Murat, Chaussain and Saint-Maurice, 1985).

This study was performed in children in this age group, to assess the changes in respiratory variables related to the concomitant use of 50% nitrous oxide and isoflurane (0.5 MAC); to assess the changes in respiratory variables related to variations in alveolar concentration of isoflurane in oxygen (0.5 MAC and 1 MAC); and to compare the respiratory depressant effect of two equipotent anaesthetic states (1 MAC): isoflurane in oxygen and isoflurane with 50% nitrous oxide.

PATIENTS AND METHODS

Anaesthesia

The study was performed in 13 children scheduled for elective surgical procedures under

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I. MURAT, M.D.; J. P. SAINT-MAURICE, M.D.; L. BEYDON, M.D.; K. MACGEE, M.D.; Département d'Anesthésie-Réanimation Chirurgicale, Hôpital Saint-Vincent-de-Paul, 74, avenue Denfert-Rochereau, 75674 Paris Cédex 14, France.

continuous extradural anaesthesia. The operations involved were either genito-urinary procedures or orthopaedic operations on the lower limb (hypospadias repair: $n = 6$; surgical correction of club foot: $n = 6$; plastic surgery of the external genital organs: $n = 1$). Mean age (±SD) was 45.6±19.3 month (range 13–75 month), mean weight 14.9±4.8 kg (range 7.4–24 kg), and mean height 97.9±17.6 cm (range 71.5–122 cm). Parental consent was obtained after a full explanation, and the study was approved by the Ethics Committee of the local hospital.

The children were not premedicated. Induction of anaesthesia was carried out using a mixture of oxygen, 50% nitrous oxide and isoflurane (to 3–3.5%) administered via a face-mask. Intubation was performed with an uncuffed tracheal tube under isoflurane anaesthesia without the use of a neuromuscular blocking drug or an opioid. After intubation, the children were allowed to breathe spontaneously through an open circuit with a low opening pressure valve. Extradural puncture was performed with a 19-gauge Tuohy needle which was inserted via the L3–4 or L4–5 lumbar space. Once the extradural space had been identified, a 24-gauge polyurethane catheter was inserted and fixed. Bupivacaine 0.25% with adrenaline 1:200000 was used throughout; a loading dose of 0.75 ml kg^{-1} was given initially. Further injections were administered either at fixed intervals according to the pharmacological characteristics of the local anaesthetic used or earlier if changes in arterial pressure or heart rate occurred (Delleur et al., 1985). The level of analgesia obtained was assessed if possible in the postoperative period.

During surgery, the ECG and oesophageal temperature were monitored continuously. Arterial pressure was measured (Dinamap) and recorded every 2 min.

The study was performed during the surgical procedure, if no haemodynamic change occurred after skin incision, while the children were breathing oxygen, 50% nitrous oxide and isoflurane (0.5 MAC).

Clinical study

The study was performed in order to assess changes in respiratory variables during three different states of anaesthesia:

(1) isoflurane 0.5 MAC in oxygen;
(2) isoflurane 0.5 MAC with 50% nitrous oxide;
(3) isoflurane 1 MAC in oxygen.

MAC for isoflurane for this age group is 1.6% (Cameron, Robinson and Gregory, 1984). We assumed that the 50% nitrous oxide MAC equivalent in the anaesthetic mixtures was 0.5 MAC and that anaesthetic states (2) and (3) were equipotent (Quasha, Eger and Tinker, 1980).

For each period of study, measurements of respiratory variables were performed at least 10 min after obtaining a stable alveolar fraction of isoflurane or at least 10 min after withdrawing or reintroducing the nitrous oxide.

At least seven successive periods were studied. The first and last measurements were performed under nitrous oxide – isoflurane anaesthesia (2). Between these two periods of study, the gas mixtures were changed randomly to assess: the effect of withdrawing or reintroducing nitrous oxide (comparison between (1) and (2)); the changes at two different MACs of isoflurane in oxygen (comparison between (1) and (3)); the respiratory depressant effect at two equipotent anaesthetic states (comparison between (2) and (3)).

Respiratory variables were compared only when obtained during two successive periods.

The total fresh gas flow was identical throughout the study in each patient.

Measurements

The concentrations of carbon dioxide and isoflurane were measured continuously, isoflurane with a calibrated infra-red analyser (Normac, Datex), and the end-expiratory fraction of carbon dioxide (FE'_{CO_2}) with a capnograph (Datex) with automatic correction for nitrous oxide. The rates of sampling were respectively 150 ml min^{-1} and 50 ml min^{-1}, and samples were measured directly from the tracheal tube. The expired carbon dioxide waveform was recorded continuously. The presence of an end-tidal plateau was verified for all patients included in the study.

Inspired gas flow was measured with a heated Fleish pneumotachograph No. 1/0 connected to a differential pressure transducer (Godart). The pneumotachograph head was inserted between the non-rebreathing valve and the tracheal tube. The internal volume was 4.7 ml. The flow signal was calibrated with room air using the flow calibration set (Godart), and tidal volume (V_T) was derived by electronic integration of the inspiratory flow signal. Tidal volume was calibrated before and after each study with room air using syringes of known volume. The temperature of

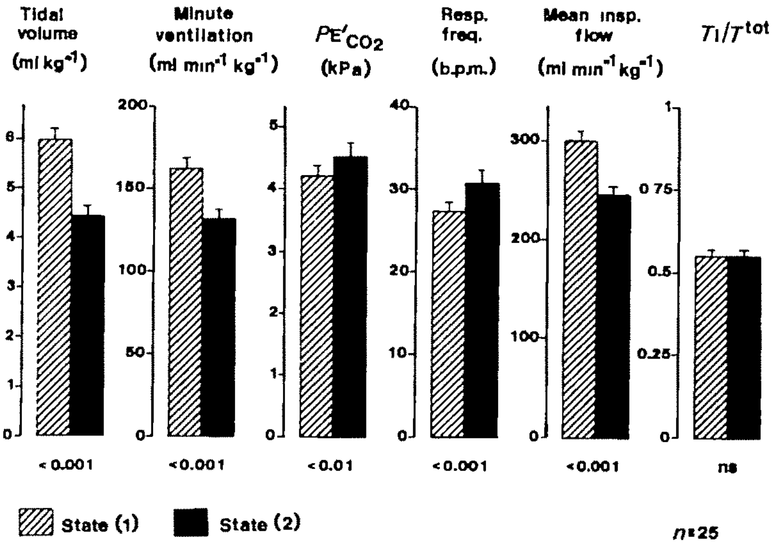

FIG. 1. Respiratory effects of nitrous oxide. Comparison between the respiratory variables obtained in 25 consecutive study periods in states (1) (isoflurane 0.5 MAC in oxygen) and (2) (isoflurane 0.5 MAC and 50% nitrous oxide).

TABLE I. *Respiratory effects of nitrous oxide* (n = 25) (*mean* ± *SEM*). *Comparison between the respiratory variables obtained in 25 consecutive study periods in state (1) (isoflurane 0.5 MAC in oxygen) and state (2) (isoflurane 0.5 MAC with 50% nitrous oxide). Statistical analysis:* t *test for paired samples*

	State (1)	State (2)	t	P
$P_{E'CO_2}$ (kPa)	4.22±0.16	4.55±0.21	3.60	< 0.01
V_T (ml kg^{-1})	6.06±0.23	4.47±0.20	12.23	< 0.001
$\dot{V}_E$ (ml kg^{-1} min^{-1})	162.17±6.83	132.95±6.16	8.03	< 0.001
f (b.p.m.)	27.39±1.24	30.81±1.69	5.31	< 0.001
$\dot{V}_I$ (ml kg^{-1} min^{-1})	296.95±10.24	245.07±9.96	8.3	< 0.001
T_I (s)	1.25±0.06	1.12±0.06	5.4	< 0.001
T^{tot} (s)	2.37±0.15	2.13±0.17	4.05	< 0.001
T_I/T^{tot}	0.547±0.022	0.551±0.020	0.38	ns

room air used for calibration ranged between 24 and 26 °C and was not different from the temperature of the inspired gas mixture. The values obtained from the flow signal and the integrated V_T were corrected according to the recommendations published by Smith (1963, 1964) in order to offset the errors introduced by the varying viscosity of the changing mixture of nitrous oxide and oxygen used in the study.

Tidal volume was recorded throughout the study on a twin-channel rapidly responding recorder (Gould–Godart). The following variables were then measured manually by averaging 10 successive breaths recorded at a speed of 750 mm min^{-1} in the steady state: inspiratory time (T_I), total respiratory time (T^{tot}), respiratory frequency (f).

The following variables were calculated: mean inspiratory flow, $\dot{V}_I$ (ml min^{-1} kg^{-1}); minute ventilation, $\dot{V}_E$ (ml min^{-1} kg^{-1}); effective inspiratory time, T_I/T^{tot}; end-tidal carbon dioxide partial pressure $P_{E'CO_2}$ (kPa). $\dot{V}_E$, V_T and $\dot{V}_I$ were corrected to body temperature and pressure saturated (BTPS).

Statistical analysis

The variables obtained were compared, initially, using an analysis of variance in order to assess whether any variations were related to the order of the study periods. The changes in the

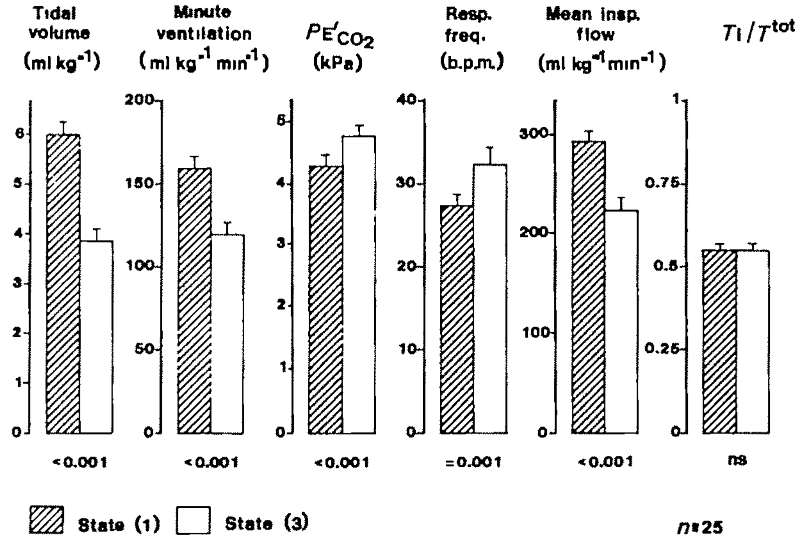

FIG. 2. Respiratory effects of isoflurane. Comparison of 25 consecutive study periods in states (1) (isoflurane 0.5 MAC in oxygen) and (3) (isoflurane 1 MAC in oxygen).

TABLE II. *Respiratory effects of isoflurane* (n = 25) (*mean* ± *SEM*). *Comparison of 25 consecutive study periods in state (1) (isoflurane 0.5 MAC in oxygen) and state (3) (isoflurane 1 MAC in oxygen)*

	State (1)	State (3)	t	P
$P\text{E}'_{CO_2}$ (kPa)	4.30 ± 0.17	4.78 ± 0.22	4.23	< 0.001
$V\text{T}$ (ml kg^{-1})	6.0 ± 0.24	3.84 ± 0.23	10.99	< 0.001
$\dot{V}\text{E}$ (ml kg^{-1} min^{-1})	160.76 ± 7.04	120.14 ± 7.61	9.81	< 0.001
f (b.p.m.)	27.44 ± 1.27	32.52 ± 2.10	3.73	= 0.001
$\dot{V}\text{I}$ (ml kg^{-1} min^{-1})	294.02 ± 10.88	223.98 ± 13.69	6.71	< 0.001
$T\text{I}$ (s)	1.30 ± 0.07	1.16 ± 0.06	2.78	= 0.01
T^{tot} (s)	2.37 ± 0.15	2.09 ± 0.21	2.63	< 0.02
$T\text{I}/T^{tot}$	0.546 ± 0.022	0.551 ± 0.022	0.33	ns

respiratory variables of two consecutive periods of anaesthesia were then compared using Student's t test for paired samples. Values of $P < 0.05$ or less were regarded as significant. Results are expressed as mean ± standard error of the mean (SEM).

RESULTS

Respiratory data

Eighty-four periods were studied in 13 children: 27 in state (1), 32 in state (2), 25 in state (3).

The effects of nitrous oxide were assessed by comparison of respiratory variables obtained at (1) and (2) (fig. 1). Twenty-five successive periods in a random order were compared. The results are expressed in table I. The addition of nitrous oxide produced a significant increase in $P\text{E}'_{CO_2}$, significant decreases in $V\text{T}$, $\dot{V}\text{E}$, $\dot{V}\text{I}$. The effective inspiratory timing was not changed, but significant decreases in both $T\text{I}$ and T^{tot}, and a significant increase in respiratory frequency, were observed.

The effect of isoflurane on respiration was assessed by comparison of respiratory variables obtained at (1) and (3) (fig. 2). Twenty-five successive periods were compared. The results are presented in table II. The increase in the alveolar concentration of isoflurane was marked by a significant increase in $P\text{E}'_{CO_2}$, significant decreases in $V\text{T}$, $\dot{V}\text{E}$, $\dot{V}\text{I}$ along with a significant increase in respiratory frequency, and significant decreases in $T\text{I}$ and T^{tot}, without change in effective inspiratory timing.

The two equipotent anaesthetic states (2) and (3) were compared in 21 successive periods (fig. 3). The results are detailed in table III. The use of isoflurane alone was marked by significant decreases in $V\text{T}$, $\dot{V}\text{E}$ and $\dot{V}\text{I}$, but no significant changes in $P\text{E}'_{CO_2}$, respiratory rate or respiratory timing were observed.

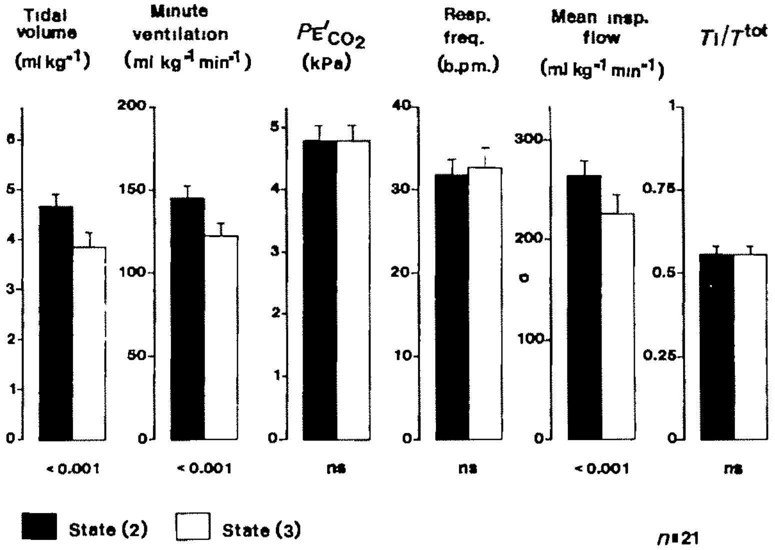

FIG. 3. Comparison of two equivalent anaesthetic states in 21 consecutive study periods at (2) (isoflurane 0.5 MAC and 50% nitrous oxide) and (3) (isoflurane 1 MAC in oxygen).

TABLE III. *Comparison of two equipotent anaesthetic states* (n = 21) (*mean* ± *SEM*) *in 21 consecutive study periods in state* (2) (*isoflurane 0.5 MAC with 50% nitrous oxide*) *and state* (3) (*isoflurane 1 MAC in oxygen*)

	State (2)	State (3)	*t*	*P*
PE'_{CO_2} (kPa)	4.79±0.23	4.81±0.23	0.27	ns
V_T (ml kg^{-1})	4.66±0.22	3.89±0.26	5.77	< 0.001
$\dot{V}_E$ (ml kg^{-1} min^{-1})	145.04±7.51	122.01±7.74	5.87	< 0.001
f (b.p.m.)	31.85±1.77	32.54±2.17	0.94	ns
$\dot{V}_I$ (ml kg^{-1} min^{-1})	262.39±14.08	221.16±15.85	4.65	< 0.001
T_I (s)	1.11±0.06	1.11±0.06	0.11	ns
T^{tot} (s)	1.97±0.08	1.95±0.09	0.42	ns
T_I/T^{tot}	0.564±0.016	0.568±0.019	0.34	ns

Haemodynamic data

Haemodynamic data were obtained in nine children. The overall analysis failed to demonstrate any significant change in heart rate or arterial pressure (table IV).

TABLE IV. *Haemodynamic data in nine children in states* (1), (2) *and* (3)

	State (1)	State (2)	State (3)	*P*
HR	112.8	114.4	119.7	ns
(beat min^{-1})	±3.7	±3.5	±4.4	
SAP	84.3	85.4	84.4	ns
(mm Hg)	±3.7	±4.7	±4.8	
MAP	53.5	53.8	53.8	ns
(mm Hg)	±3.0	±3.1	±3.3	
DAP	36.9	36.5	34.5	ns
(mm Hg)	±2.8	±2.7	±2.4	

Duration of anaesthesia

The interval between the first and last period of study (state 2) was never less than 70 min.

The comparison of respiratory indices obtained demonstrated a marked reduction in respiratory frequency with a reduction in both T_I and T^{tot} without change in effective inspiratory timing (table V). This reduction in respiratory frequency, without change in tidal volume, was responsible for the significant decrease in $\dot{V}_E$ with a significant increase in PE'_{CO_2}.

DISCUSSION

Methods

Respiratory measurements were performed under lumbar extradural anaesthesia. This technique is commonly used in our hospital to decrease

TABLE V. *Comparison of respiratory variables obtained at the same state of anaesthesia (2). Mean time interval between the two periods was not less than 70 min while children were breathing spontaneously*

	Isoflurane 0.5 MAC with 50% nitrous oxide			
	Initial period	End period	t	P
$P\text{E}'_{CO_2}$ (kPa)	4.27 ± 0.35	4.85 ± 0.32	2.69	< 0.05
$V\text{T}$ (ml kg^{-1})	4.57 ± 0.36	4.78 ± 0.26	0.89	ns
$\dot{V}\text{I}$ (ml kg^{-1} min^{-1})	277.08 ± 23.3	251.68 ± 19.7	2.70	< 0.05
$T\text{I}$ (s)	1.02 ± 0.09	1.20 ± 0.10	2.56	< 0.05
T^{tot} (s)	1.83 ± 0.13	2.12 ± 0.14	3.07	< 0.05
$T\text{I}/T^{tot}$	0.56 ± 0.03	0.56 ± 0.03	0.49	ns
f (b.p.m.)	34.61 ± 2.99	29.9 ± 2.82	2.59	< 0.05
$\dot{V}\text{E}$ (ml kg^{-1} min^{-1})	152 ± 11.57	139 ± 9.26	2.56	< 0.05

the requirement for anaesthetic, to assure a prompt, safe and rapid recovery and to provide postoperative analgesia. In young children, extradural anaesthesia has to be performed under general anaesthesia and, usually, light general anaesthesia is maintained during the surgical procedure. In all cases, the level of analgesia was sufficient to avoid clinical or haemodynamic manifestations of pain and, thus, it can be considered that this study was performed in "unstimulated" children. The most cephalad segmental level of anaesthesia obtained by this technique (puncture at L3–4 or L4–5 space) was below T8 in all patients. The segmental level of analgesia was assessed at the end of surgery when this was possible.

It is commonly accepted that blockade up to the level of T8 is in itself unlikely to interfere with respiratory function during and after operation (Hatch, Hulse and Lindahl, 1984). Furthermore, the concentration of bupivacaine used (0.25%) does not generally produce clinical evidence of motor blockade. The method used also allowed measurement of the respiratory variables without any increase in the duration of the anaesthetic.

Respiratory effects of nitrous oxide

The respiratory effects of nitrous oxide were assessed by studying the respiratory variables obtained under isoflurane 0.5 MAC either in oxygen or in 50% nitrous oxide, without change in the total fresh gas flow.

The addition of 50% nitrous oxide to 0.5 MAC isoflurane produced a decrease in alveolar ventilation with a significant increase in $P\text{E}'_{CO_2}$ and a significant decrease in $\dot{V}\text{E}$. This effect was attributable solely to the nitrous oxide, since no drug other than the nitrous oxide and isoflurane was used either for premedication or during anaesthesia. This reduction in alveolar ventilation was related to a decrease in tidal volume and mean inspiratory flow. However, the use of nitrous oxide was associated with a significant increase in respiratory frequency with concomitant decreases in $T\text{I}$ and T^{tot}, but without change in effective inspiratory timing.

These results differ from the study reported by Wren and colleagues (1984) which analysed the effects of nitrous oxide on respiratory patterns during halothane anaesthesia in children. Three explanations can be suggested for the differences; first, the concentration of nitrous oxide used was greater than that used in the present study (60% *v.* 50%). Second, the study by Wren and colleagues was performed at 1 MAC halothane and, third, the children were premedicated with papaveretum or thiopentone. However, the respiratory variables reported by Wren and colleagues (1984) at 1 MAC halothane in oxygen are accounted for mainly by a marked reduction in $\dot{V}\text{E}$ and $V\text{T}$ when compared with our values at 0.5 MAC isoflurane. The respective values for halothane 1 MAC *v.* isoflurane 0.5 MAC in oxygen are 3.05 ml kg^{-1} *v.* 6.06 ml kg^{-1} for $V\text{T}$ and 84.09 *v.* 162.17 ml kg^{-1} min^{-1} for $\dot{V}\text{E}$.

A direct measurement of the alveolar concentration of nitrous oxide was not obtained in the present study. However, using an infra-red analyser, Wren and colleagues (1984) demonstrated that decreases and increases in alveolar concentration after the withdrawal or addition of nitrous oxide occur rapidly and that, usually, a stable alveolar concentration is obtained in less than 3 min. The 10-min time interval between the two measurements in the present study, therefore, ensures that a steady state had been achieved.

Respiratory effects of isoflurane

The respiratory depressant effect of isoflurane was assessed by studying the respiratory variables obtained under isoflurane 0.5 MAC or 1 MAC in oxygen. The increase in the alveolar concentration of isoflurane was associated with a decrease in alveolar ventilation. However, the decrease in $\dot{V}_E$ was solely the result of a marked reduction in V_T. Therefore, minute ventilation decreased significantly despite a significant increase in respiratory rate.

These changes were related to a marked decrease in the driving output of the respiratory centre without a change in the effective inspiratory timing. Thus, the changes reflect the central respiratory depressant effect of isoflurane.

Similar results were previously reported by Eger and co-workers (1972) in adult patients. At 1 MAC isoflurane in oxygen, respiratory frequency was moderately increased, but no further changes occurred as the alveolar concentration of isoflurane was increased.

In children, we did not find any change in respiratory frequency with isoflurane 0.8, 1.1, 1.4 MAC in 50% nitrous oxide (Murat, Chaussain and Saint-Maurice, 1985). Nevertheless, although the respiratory depressant effect of 1 MAC of isoflurane is not negligible, it may still be used in spontaneously breathing children during short surgical procedures.

Comparison at an equivalent MAC multiple

A comparison between 1 MAC isoflurane in oxygen or isoflurane in nitrous oxide was made in order to assess the possible "sparing effect" of nitrous oxide. This was reported by Fourcade and associates (1971) in adult patients. They reported that the net result of substituting nitrous oxide for an equal MAC fraction of isoflurane was to produce a smaller increase in Pa_{CO_2} than expected. This was because of a greater increase in respiratory rate in patients anaesthesized with nitrous oxide and isoflurane.

The same results were also reported by Dolan and co-workers (1974) in adult patients. At 1.09 MAC of a mixture of 70% nitrous oxide and isoflurane, the respiratory rate was increased by up to 240% of the awake values.

However, when respiratory variables at an equivalent MAC either of isoflurane in oxygen or of a mixture of 70% nitrous oxide and isoflurane were compared in Dolan's study, the mixture of nitrous oxide and isoflurane failed to ameliorate the respiratory depression produced by the isoflurane alone. It is worth noting that the decrease in tidal volume was identical in both groups of this study.

Our results differ markedly from both of these reports. Both $P_{E'CO_2}$ and respiratory rate were unchanged when the two anaesthetic states were compared. On the other hand, anaesthesia with isoflurane alone was found to be associated with significant decreases in V_T, $\dot{V}_I$ and $\dot{V}_E$ when compared with the same MAC of isoflurane and nitrous oxide. However, no change was found in the effective inspiratory timing.

These results suggest that the central respiratory depressant effect of isoflurane was greater than that of nitrous oxide in children. The addition of opioids either as premedication or during the surgical procedure may modify these results (Wren et al., 1984).

In summary, our results demonstrated a "sparing effect" of nitrous oxide during isoflurane anaesthesia, but the mechanism involved in children seems to differ from that reported in adult patients.

Haemodynamic changes

No haemodynamic changes were found when the three states of anaesthesia were compared: heart rate increased slightly but not significantly and arterial pressure remained unchanged.

In children, less than 10 years of age, Wren and colleagues (1985) found that, in half of the 138 patients studied, the heart rate remained either stable or increased by less than 10%. In that study, the stability of the heart rate in children who had received isoflurane alone was apparent. Similar results were reported by Neal and associates (1984). In children aged 5–26 weeks, Friesen and Lichtor (1983) demonstrated a decrease in both heart rate and arterial pressure following induction of anaesthesia with isoflurane. These results contrast with those previously reported in adults (Forrest, 1982a; Rolly, Versichelen and Moerman, 1984). In adult patients isoflurane tends to increase heart rate. Whether an increase occurs depends on the heart rate before anaesthesia: a high pre-anaesthetic rate predisposes the heart to a decrease in rate rather than an increase (Forrest, 1982b).

Extradural anaesthesia was not associated with significant haemodynamic changes (Delleur et al., 1985) in children. However, the combination of general and extradural anaesthesia did not allow us to assess the precise changes produced by isoflurane or nitrous oxide alone in children. Nevertheless, the absence of significant haemodynamic changes allowed us to eliminate this factor in changes in the ventilatory patterns observed.

Duration of anaesthesia

Respiratory rate decreased significantly when the initial and the last period at the same level of anaesthesia (2) were compared. No significant change was found for tidal volume and effective inspiratory timing. Mean inspiratory flow decreased significantly. These changes may be related to an expected increase in airway and pulmonary resistance. Changes in airway resistance could be related to tracheal secretions during spontaneous breathing with an unhumidified circuit and changes in pulmonary resistance have been reported by Rehder and colleagues (1974) during isoflurane anaesthesia in adult patients.

CONCLUSION

Addition of nitrous oxide to isoflurane produced a decrease in alveolar ventilation despite a significant increase in respiratory rate.

The increase in the alveolar concentration of isoflurane was associated with a significant decrease in alveolar ventilation, with a marked reduction in tidal volume, and with a moderate increase in respiratory rate.

The net result of the substitution of nitrous oxide for an equal MAC fraction of isoflurane was to produce a smaller decrease in tidal volume responsible for a smaller decrease in minute ventilation, with no change in respiratory rate.

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CONTRIBUTION OF EXTRADURAL TEMPERATURE TO SHIVERING DURING EXTRADURAL ANAESTHESIA

A. J. WALMSLEY, A. H. GIESECKE AND J. M. LIPTON

SUMMARY

Thirty patients having postpartum tubal ligation under extradural anaesthesia were studied. All received bupivacaine at 4 °C initially and the incidence of shivering (47%), and the extradural temperatures measured with a small thermistor threaded into the extradural catheter, were recorded. To eight patients in whom the resultant shivering was marked, further bupivacaine warmed to 41 °C was injected. In four of these patients, shivering was stopped. The results suggest that thermosensitive tissue within the spinal canal contributes to the shivering observed in association with extradural anaesthesia.

Shivering is a recognized complication of extradural anaesthesia (Downing, 1969; Waters, Rosen and Perkins, 1970), and various mechanisms have been suggested: a decrease in core temperature as a result of the peripheral vasodilatation caused by the sympathetic blockade; an effect of the anaesthetic after absorption into the systemic circulation; a differential inhibition of afferent thermoreceptor fibres within the spinal cord that causes an erroneous indication of a decrease in peripheral temperature (Fruhstorter, Nolte and Hensel, 1974), and a direct effect of cold anaesthetic solution on thermosensitive neurones within the spinal cord. Although peripheral vasodilatation does occur, there is no evidence that it is accompanied by the decrease in core temperature necessary to initiate shivering. Cutaneous vasodilatation also occurs in association with subarachnoid analgesia but, since shivering has not been reported, that hypothesis is unlikely. Toxic effects of bupivacaine on hypothalamic centres are unlikely, since similar quantities of the drug injected elsewhere in the body (for example, brachial plexus blockade or i.v. regional analgesia) rarely induce shivering, even in the presence of other signs of central toxicity. Subarachnoid blockade would be expected to affect thermoreceptor fibres but, as stated above, intrathecal analgesia does not result in shivering. Furthermore, evidence for a differential effect on thermal afferent inputs has only been reported for ulnar nerve blockade with mepivacaine (Fruhstorter, Nolte and Hensel, 1974) and not in association with extradural anaesthesia. On the other hand, there is abundant evidence that thermosensitive structures exist within the spinal cord of various mammalian species (Kosaka, Simon and Thauer, 1965; Jessen and Mayer, 1971; Fuller, Horowitz and Horowitz, 1977), and it has been suggested that shivering can be activated by local cooling of the spinal canal in man (Ponte, Collett and Walmsley, 1986). The aims of the present study were: to determine the incidence of shivering when cold bupivacaine was injected to the extradural space; to correlate shivering with the temperature changes within the extradural space caused by these injections; and to determine whether shivering induced by the injection of cold anaesthetic solution could be reversed by the subsequent administration of warmed anaesthetic solution.

PATIENTS AND METHODS

Following approval by the Institutional Review Board, 30 patients (mean age 27.2 yr ± SEM 0.82, range 21–36 yr) who were scheduled to undergo tubal ligation under extradural anaesthesia 24–48 h postpartum gave informed consent to

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A. J. WALMSLEY,* M.B.B.S., F.F.A.R.C.S., A. H. GIESECKE, JR, M.D. (Department of Anesthesiology); J. M. LIPTON, PH.D. (Department of Physiology); University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, TX 75235, U.S.A.

*Present address for correspondence: Department of Anaesthesia, King's College Hospital, Denmark Hill, London SE5.

participate in the study. No patient was febrile nor had any received medication in the preoperative period. All were clinically normovolaemic with a normal haemoglobin concentration. An i.v. cannula was inserted under local anaesthesia, and an infusion of lactated Ringer's solution 1 litre warmed to 37 °C commenced. The patient was placed in the lateral position, and the lumbar region was cleaned with iodine solution. The extradural space was located with a 16-gauge Tuohy needle and an air-filled syringe, using the loss of resistance technique. An 18-gauge Concord extradural catheter with a thermistor probe (Yellow Springs Instruments (YSI) Series 511 sterilized with ethylene oxide) threaded to its tip was inserted. To reduce heat exchange, the extradural catheter was shortened to 40 cm before the insertion of the thermistor and was not taped to the patient's back (Walmsley, Ponte and Wright, 1984).

The temperature of the ambient air was recorded throughout the procedure, and a record of core temperature was obtained by placing a thermistor probe (YSI 409) over the axillary artery. Measurements of skin temperature were recorded by means of thermistor probes at four sites: the outer aspect of the lower leg; the thigh; the deltoid muscle; and the chest. Mean skin temperature (MST) was calculated using the formula described by Ramanathan (1964):

$$\text{MST} = 0.3\ (\text{chest} + \text{deltoid}) + 0.2\ (\text{thigh} + \text{leg})$$

All measurements were taken before the insertion of the extradural catheter, before the injection of the test dose of anaesthetic, and at 5-min intervals throughout the study.

All patients received, via the extradural catheter, a test dose of 0.5% plain bupivacaine 4 ml, cooled to 4 °C in a water bath maintained at this temperature, followed by doses of 7 and 5 ml at the same temperature. If shivering did not occur after any of the first three injections, an additional 5 ml of cold anaesthetic was given. Extradural temperature was monitored continuously after each injection until it returned to baseline. The extradural temperature was allowed to return to 37 °C before a subsequent dose was given. Shivering was recorded by electromyography with electrodes placed over the muscles of the anterior shoulder girdle. In certain patients, bupivacaine 5 ml warmed to 41 °C was given in an attempt to reverse shivering induced by the administration of the cold solution.

The electrocardiogram was monitored throughout the study, and arterial pressure was recorded (Dinamap) at the same time intervals as air, core, and skin temperatures. The dermatome levels to which neural blockade extended were noted at 15-min intervals. If necessary, additional lactated Ringer's solution (no more than 500 ml) at 37 °C was infused i.v. to counteract systemic arterial hypotension. Once blockade to the T6 sensory level or higher had been achieved and surgery could commence, the study was terminated.

RESULTS

Fourteen of the 30 patients (47%) shivered after one or more of the injections of cold anaesthetic solution. There were no significant differences between those patients who shivered and those who did not, with respect to any of the variables in table I. The mean temperatures were calculated by averaging measurements taken at 5-min intervals from immediately before the placement of the extradural catheter until the end of the study. Likewise, although there were increases in mean skin and axillary temperatures from the insertion of the catheter to the last reading in both the shivering and non-shivering groups (table II),

TABLE I. *Comparison of data of shivering and non-shivering patients. Mean values ± standard error of the mean (SEM)*

	Age (yr)	Weight (kg)	Volume of anaesthetic solution (ml)	Level of block (thoracic segment)	Ambient temperature (°C)	Mean skin temperature (°C)	Axillary temperature (°C)
Shivering	28.69	66.12	21.86	5.36	20.74	32.21	36.91
(n = 14)	±1.55	±3.63	±0.91	±0.37	±0.21	±0.21	±0.22
Non-shivering	26.00	61.20	21.93	6.31	20.90	32.16	36.60
(n = 16)	±0.71	±2.70	±0.93	±0.53	±0.22	±0.20	±0.10
P (t test)	0.132	0.282	0.951	0.162	0.608	0.883	0.217

TABLE II. *Pre-extradural and final values of mean skin and axillary temperatures in shivering and non-shivering patients (mean values ± SEM).* t = *difference between means ± SED (standard error of the difference)*

	Mean skin temperature (°C)			Core temperature (°C)		
	1st	Last	*t*	1st	Last	*t*
Shivering	31.86	32.27	0.41	36.75	36.94	0.19
($n = 14$)	±0.20	±0.28	±0.28	±0.18	±0.25	±0.14
P		0.167			0.206	
Non-shivering	31.70	32.08	0.38	36.24	36.64	0.40
($n = 16$)	±0.24	±0.25	±0.22	±0.21	±0.14	±0.23
P		0.097			0.102	

TABLE III. *Time (min) (mean ± SEM) from extradural injection to return of extradural space temperature to 37 °C and time from injection to start of shivering for first four cold doses given*

	Dose 1 (4 ml)	Dose 2 (7 ml)	Dose 3 (5 ml)	Dose 4 (5 ml)
Injection to	7.36	13.3	11.0	11.1
return to 37 °C	±0.43	±0.51	±0.49	±0.50
(min)	($n = 30$)	($n = 30$)	($n = 30$)	($n = 9$)
Injection to		3.46	4.36	4.2
start of shivering		±2.05	±0.52	±0.79
(min)		($n = 5$)	($n = 6$)	($n = 7$)

neither these increases nor the differences in increase between the two groups were significant.

Injections of cold anaesthetic solution caused extradural temperatures to decrease to less than 20 °C and to remain below 37 °C for several minutes. The larger the volume given, the longer the extradural temperature remained less than 37 °C. When shivering occurred (defined as an episode which lasted for longer than 30 s), it began within an average of 3.5–4.4 min after injection (table III). No patient shivered after the first dose alone, but the number of patients that shivered increased with each subsequent dose of cold solution. In each instance, shivering was noted by the patient as well as recorded on the electromyogram. Episodes of shivering lasted 1–22 min and in five patients shivering was still present when surgery commenced.

Bupivacaine warmed to above body temperature was administered 11 times to eight patients in whom shivering had been present for longer than 5 min. In four of these patients in whom the temperature of the solution was 39–40 °C, shivering stopped within 0.5–2 min and did not resume for 7 or 8 min. Cessation of shivering corresponded well with the periods in which the extradural temperature had increased. The extradural temperature returned to baseline in 7.5–10.7 min. Figure 1 shows two successful tests in one of these patients. Six attempts to decrease shivering in the other four patients were unsuccessful. (Four of these failures occurred early in the study when the bupivacaine solution was heated insufficiently to prevent its cooling to less than body temperature by the time it had entered the extradural space.)

DISCUSSION

Although the injection of local anaesthetic solution at 4 °C to the extradural space is not usual clinically, it was considered justified to enhance the physiological response which has previously been noted with solutions at room temperature. The overall incidence of shivering in this series was comparable to those reported previously (Downing, 1969; Waters, Rosen and Perkins, 1970; Ponte, Collett and Walmsley, 1986). Evidence that cooling the spinal cord in man produces shivering has been reported only recently (Ponte, Collett and Walmsley, 1986). Studies in rabbits have shown that, in this species, it takes several minutes for the temperature of the extradural space to return to normal after injections of cold fluid (Ponte and Simpson,

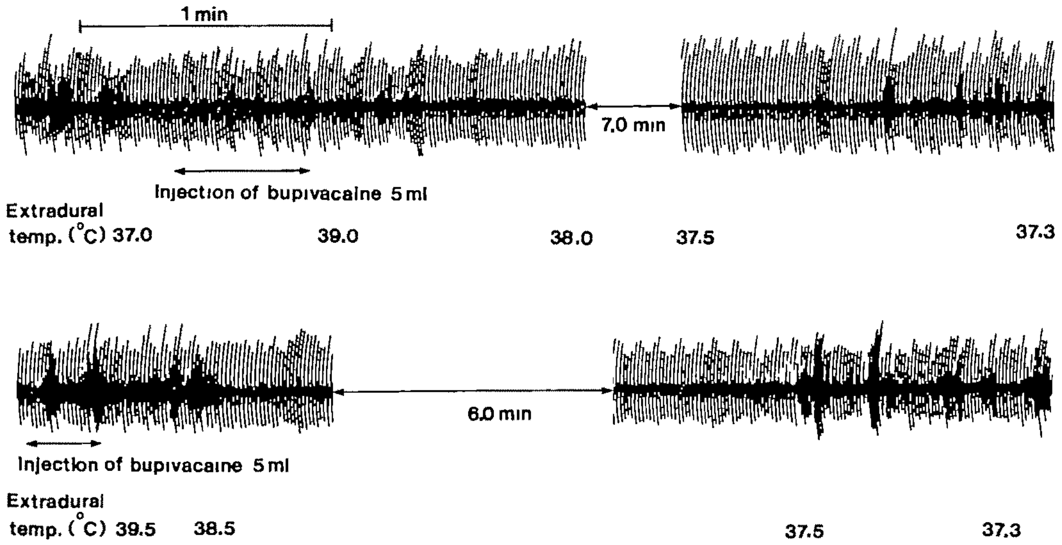

FIG. 1. Electromyographic evidence of cessation of shivering episodes, and extradural temperature, in a single patient receiving warmed bupivacaine on two occasions. Large amplitude spikes represent ECG artefact.

1985). Our study has shown that even small volumes of cold anaesthetic solution can decrease extradural temperature for prolonged periods. In all patients in whom shivering occurred, it started during this period. However it is not known why the shivering did not begin immediately—when the decrease in temperature was greatest, rather than on average about 4 min later.

Assuming the presence of temperature receptors in the spinal cord, one would expect that, having evoked shivering by cooling the cord, one would be able to stop it by warming the cord. In five of seven attempts in which the extradural temperature was increased, shivering stopped. The timing and duration of the cessation of shivering were remarkably consistent in the five instances and correlated well with the increase in extradural temperature. Shivering resumed in all cases as the extradural temperature approached baseline.

Shivering is a physiological mechanism to increase heat production. Its initiation depends on the interaction of three factors: input from peripheral cold receptors, input from non-hypothalamic thermosensitive neurones (e.g., spinal cord), and the temperature of the hypothalamus. The hypothalamus acts as the integrating centre for such thermal inputs.

Hypothalamic temperature may decrease as a result of heat loss consequent on cutaneous vasodilatation or of the infusion of cold i.v. fluids. In this study, central temperature did not decrease in any of our patients. Rapid i.v. infusion of solutions kept at room temperature may decrease central temperature, but in this study this variable was eliminated by warming all i.v. fluids to 37 °C.

Apart from the hypothalamus, the existence of other deep body temperature receptors has been suggested. Receptors in other parts of the central nervous system, namely, the midbrain reticular formation and the spinal cord, have been shown to initiate shivering. In several mammalian species, local cooling of the spinal cord produces shivering and vasoconstriction, and shivering as a result of peripheral cooling can be enhanced by direct cooling of the spinal cord. Selective warming of the spinal cord, on the other hand, suppresses ongoing shivering and induces cutaneous vasodilatation (Hemingway, 1963; Kosaka, Simon and Thauer, 1966; Jessen and Mayer, 1971; Fuller, Horowitz and Horowitz, 1977). Evidence for temperature sensors in the large veins and in the gut is inconclusive.

It is unclear why some subjects shivered and others did not, despite low temperatures in the extradural space. One possible explanation could be in the height of sensory block achieved. The mean height of blockade in the shivering group was one thoracic segment higher than in the non-shivering group. Although this difference is small, this could affect the incidence of shivering in one of two ways. First, when a higher segment is reached, more of the spinal cord is exposed to the cold sensory stimuli providing, perhaps, a greater neuronal input to the hypothalamus. Alternatively, there may be a higher density of thermosensitive neurones in the spinal canal nearer the brain. It is possible, however, that there are many unknown mechanisms subserving the shivering and that the injection of cold local anaesthetic solutions is only one of these. The same theory would also explain why solution at 41 °C did not stop shivering in all patients.

Although recent work has suggested that spinal canal thermosensitive tissue exists (Ponte, Collett and Walmsley, 1986), our observations that temperature changes within the extradural space can be marked and that shivering can be stopped by increasing the temperature in the extradural space provide further evidence of the importance of thermosensitive tissue outside the hypothalamus in the maintenance of body temperature. From a practical point of view, warming of i.v. fluids and local anaesthetic solutions to 37 °C before injection should reduce the incidence of shivering associated with extradural anaesthesia.

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INFLUENCE OF EXTRADURAL BLOCKADE AND EPHEDRINE ON TRANSCUTANEOUS OXYGEN TENSION

J. A. ODOOM, I. L. SIH, J. G. BOVILL, B. VAN DER BROEK
AND J. OOSTING

SUMMARY

The influence of lumbar extradural blockade with 0.5% plain bupivacaine on transcutaneous oxygen tension (Ptc_{O_2}) *and skin temperature was studied in 20 patients, 10 scheduled for vascular surgery and 10 for urological surgery. At the time of maximum extent of blockade, mean arterial pressure (MAP) had decreased significantly* ($P < 0.001$) *from 96.6±18.8 mm Hg to 69.5±10.1 (mean±SD) in the vascular group and from 88.0±14.7 mm Hg to 71.1±12 mm Hg in the urological group. In the vascular group* Ptc_{O_2} *decreased significantly in the ischaemic* ($P < 0.01$) *and non-ischaemic* ($P < 0.001$) *limbs. In the urological group, there was a significant* ($P < 0.001$) *decrease in* Ptc_{O_2} *in both limbs. There was no change in cutaneous temperature in the ischaemic limbs (vascular group), but the temperature in the non-ischaemic limbs increased significantly* ($P < 0.01$)*. In the urological group, the cutaneous temperature increased significantly* ($P < 0.001$) *in both limbs. When ephedrine 10 mg was administered i.v., MAP increased significantly* ($P < 0.001$) *in both groups to pre-blockade values. This was accompanied in both groups by significant increases in* Ptc_{O_2}*, but not by a change in skin temperature. There was a significant correlation between change in MAP and change in* Ptc_{O_2} *in both groups after ephedrine.*

Patients with incipient gangrene and severe rest pain often require continuous extradural, or regional, blockade (Smith, Fischer and Scott, 1984), with local anaesthetics to control their pain. Additionally, the technique improves limb blood flow, increases skin temperature and makes it possible for the dressing of wounds and physiotherapy to be carried out with less discomfort. Lumbar extradural blockade may also be used to predict whether subsequent surgical or chemical sympathectomy is likely to be effective.

However, extradural analgesia can cause systemic hypotension (Dagnino and Prys-Roberts, 1984), and influence lower limb blood flow.

Transcutaneous oxygen tension (Ptc_{O_2}) is influenced by variations in systemic arterial pressure (Eickhoff, Ishihara and Jacobsen, 1980; Eickhoff and Jacobsen, 1982) and blood flow (Tonnesen, 1978; Eickhoff and Jacobsen, 1980).

We have, therefore, investigated the effect of hypotension on Ptc_{O_2} in patients receiving extradural blockade.

PATIENTS AND METHODS

Twenty surgical patients (10 vascular and 10 urological) were studied before surgery. All patients gave informed consent to participate in the study. None had pulmonary disease, none was premedicated.

Selection of patients

Vascular group. Patients were included in the study if they had evidence of unilateral ischaemic vascular disease as determined by history, physical examination, translumbar aortography and standard vascular laboratory tests (Raines et al., 1976). These included evaluation of claudication

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J. A. ODOOM, M.D., I. L. SIH, M.D., J. G. BOVILL,* M.D., F.F.A.R.C.S.I. (Department of Anaesthesia); J. OOSTING, PH.D. (Department of Medical Physics); B. VAN DER BROEK; University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

*Present address: Department of Anaesthesia, University Hospital, University of Leiden, Rijnsburgerweg 10, 2333 AA Leiden, the Netherlands.

Correspondence to J. A. Odoom.

by treadmill exercise, measurement of arterial pressures in arm, thigh, calf and ankle and pulse volume recording (PVR) using a Doppler ultrasonic technique (Yao, 1970). Ankle pressure index was calculated from the ratio of ankle to arm systolic arterial pressures. Ankle pressure index has been shown to correlate significantly with the degree of vascular occlusion found by arteriography (Yao, Hobbs and Irvine, 1969). All tests were performed before and after exercise.

Limbs with impending or frank gangrene, exercise-induced pain relieved by rest (claudication) or an ankle pressure index less than 1, were categorized as ischaemic. Patients with bilateral ischaemia were excluded.

Urological group. None of the patients in this group had a history of intermittent claudication. The absence of ischaemic vascular disease was further assessed by physical examination and Doppler ultrasonic flow measurements. Treadmill exercise tests and translumbar aortography were not performed.

Transcutaneous oxygen tension (Ptc_{O_2}) in the lower limbs was measured using a TCM 1 TC oxygen monitor (Radiometer, Copenhagen) and recorded continuously (Gould Inc., Cleveland Ohio, U.S.A.). The skin temperature of the limbs was measured with Telethermometer probes (Yellow Springs Instrument Co. Inc., Yellow Springs Ohio, U.S.A.) applied 2–5 cm distant from the Ptc_{O_2} electrodes. The electrocardiogram (ECG) and the heart rate (HR) were displayed continuously. Mean arterial pressure (MAP) was recorded non-invasively every 5 min using an Omega 1000 automatic pressure recorder (Invivo Research Laboratories Inc., Tulsa Oklahoma 74145, U.S.A.).

A catheter was inserted to the lumbar extradural space at the L2–3 space and the initial (baseline) measurements made. Fifteen millilitre of 0.5% plain bupivacaine was then injected through the catheter and the various indices measured continuously until maximum blockade was established. Ephedrine 10 mg was given i.v. and the measurements continued for a further 30 min. MAP, HR, Ptc_{O_2} and temperature during maximum extradural blockade, and at the peak effect of the ephedrine, were noted. All measurements were obtained in an induction room with the ambient temperature maintained at 22 °C. Four patients in whom blockade was unilateral or incomplete were excluded from further study.

Statistical analysis was performed using a paired t test. A value of $P < 0.05$ was considered significant. Values are presented as mean ± SD.

RESULTS

Patient characteristics are summarized in table I. The groups were comparable with respect to age, weight, height and sex distribution.

The mean changes in MAP, Ptc_{O_2} and cutaneous temperature before and after extradural blockade, and after the administration of ephedrine, are shown in tables II (vascular group) and III (urological group).

Changes after extradural blockade

The average times to maximum extradural blockade, as judged by motor blockade, were 30 ± 8.5 min and 31.6 ± 9.2 min in the vascular and urological groups, respectively. At this time, MAP had decreased significantly from 96.6 ± 18.8 mm Hg to 69.5 ± 10.1 mm Hg in the vascular group (table II) and from 88 ± 14.7mm Hg to 71.1 ± 12 mm Hg in the urological group (table III). This was associated with a significant decrease in Ptc_{O_2} in the ischaemic ($P < 0.01$) and non-ischaemic ($P < 0.001$) limbs in the vascular group. There was a similar decrease ($P < 0.001$) in both limbs in the urological group. In the vascular group, there were no significant changes in cutaneous temperature in the ischaemic limb. There was a significant ($P < 0.01$) increase in temperature in the non-ischaemic limb. In the urological group, there was a significant ($P < 0.001$) increase in cutaneous temperature.

Changes after administration of ephedrine

Ephedrine significantly increased MAP from 69.5 ± 10.1 mm Hg to 96.9 ± 9.5 mm Hg in the vascular group (table II) and from 71.1 ± 12 mm Hg to 89.8 ± 12.4 mm Hg in the urological group (table III).

TABLE I. *Patient characteristics (mean ± SD)*

	Vascular group	Urological group
No. of patients	10	10
Male/female	8/2	9/1
Age (yr)	69.1 ± 6.7	68.7 ± 9.3
Weight (kg)	72.7 ± 10.8	72.6 ± 11
Height (cm)	173.5 ± 8.8	174.6 ± 5.1

TABLE II. *Mean arterial pressure (MAP), transcutaneous oxygen tension* ($P\text{tc}_{O_2}$) *and temperature in the lower limbs before (I) and after maximum extradural blockade (II) and after an i.v. administration of ephedrine 10 mg (III) in 10 vascular patients*

	Mean arterial pressure (mm Hg)			Transcutaneous oxygen tension (mm Hg)						Temperature (°C)					
				Ischaemic limb			Non-ischaemic limb			Ischaemic limb			Non-ischaemic limb		
Patient	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	70	47	93	50	21	25	70	54	68	29.5	32.5	32.5	30.4	33.6	33.6
2	85	83	97	15	15	20	65	55	68	31.3	30.4	30.4	31.6	32.7	32.7
3	97	65	93	30	10	10	68	50	60	30.5	30.5	31	32.6	32.7	32.7
4	127	68	113	10	10	10	60	52	65	30.2	29.6	30.1	32.3	33.4	33.4
5	113	83	104	50	31	35	68	48	68	29.8	30.8	30.8	28.8	33.2	33.1
6	100	67	80	8	7	7	72	56	66	30	33.3	33.3	32.4	34.4	35
7	73	62	100	15	10	12	71	40	80	31.6	32.4	32.4	30.2	33.8	33.7
8	120	77	93	39	8	7	54	40	65	33.5	34.2	34.2	28.5	33.8	33.1
9	103	73	110	50	40	44	69	35	58	32.2	34.4	34.4	34.4	32.9	33.9
10	78	70	87	66	53	58	65	40	78	31.2	30.3	29.4	29.2	33.5	33.5
Mean	96.6	69.5	96.9	32.7	20.5	22.2	66.2	47	67.6	31	31.8	31.9	30.9	33.5	33.5
±SD	18.8	10.1	9.5	18.5	14.9	16.7	5.5	7.6	6.9	1.2	1.7	1.8	1.7	0.8	0.6
P		0.001	0.001		0.01	0.02		0.001	0.001		ns	ns		0.01	ns

TABLE III. *Mean arterial pressure (MAP), transcutaneous oxygen tension* ($P\text{tc}_{O_2}$) *and temperature in the lower limb before (I), after maximum extradural blockade (II) and after an i.v. administration of ephedrine 10 mg (III) in 10 urological patients*

	Mean arterial pressure (mm Hg)			Transcutaneous oxygen tension (mm Hg)						Temperature (°C)					
				Left limb			Right limb			Left limb			Right limb		
Patient	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	67	50	70	62	54	74	70	62	68	31.4	33	35.5	31.6	34	34.6
2	73	65	78	68	60	65	70	48	70	30	35.6	35	30	35.4	35.4
3	74	67	82	49	41	50	52	38	56	28.5	29.7	29.8	29	29.4	34
4	100	87	100	64	51	67	65	62	64	27.5	29.8	29.2	32.2	31	32
5	90	83	98	52	45	60	57	35	72	30	34.7	35	31	34.6	34.5
6	75	64	83	70	58	70	60	54	69	27.4	35	34.9	27.4	34.5	34.8
7	100	80	102	78	54	60	60	50	78	28.6	33	33	28.6	33.6	32
8	100	82	95	69	35	70	58	47	58	30.4	34	33.8	29.6	34	33.6
9	108	73	108	70	61	65	60	53	77	29.5	35.2	33.9	29	35.8	35
10	97	60	82	75	51	68	65	56	75	29.5	35.2	33.9	30.5	34.6	34.5
Mean	88	71.1	89.8	65.7	51	65.4	61.7	50.5	68.7	29.4	33.5	33.3	29.9	33.7	34
±SD	14.7	12.0	12.4	10.8	8.4	6.7	5.8	8.8	7.5	1.4	2.1	2.1	1.5	2.0	1.2
P		0.001	0.001		0.001	0.001		0.001	0.001		0.001	ns		0.001	ns

In the vascular group, $P\text{tc}_{O_2}$ increased significantly in both the ischaemic ($P < 0.02$) and non-ischaemic limbs ($P < 0.001$). In the urological group, $P\text{tc}_{O_2}$ increased significantly ($P < 0.001$) in both limbs. There was no significant change in cutaneous temperature in either limb of either group after the administration of the ephedrine.

In the vascular group, the change in MAP correlated well with changes in $P\text{tc}_{O_2}$ in the ischaemic limb ($r = 0.64$; $P < 0.01$)., and the non-ischaemic limb ($r = 0.76$; $P < 0.001$) (fig. 1). A similar correlation between change in MAP and change in $P\text{tc}_{O_2}$ ($r = 0.77$; $P < 0.001$) was found in the urological group (fig. 2).

DISCUSSION

Vascular tone is controlled by the level of sympathetic activity. In the normal subject, lumbar sympathetic blockade, whether produced by surgical or chemical denervation, causes vascular dilatation, a decrease in regional vascular resistance and, in the absence of a large decrease in arterial pressure, increases in capillary blood

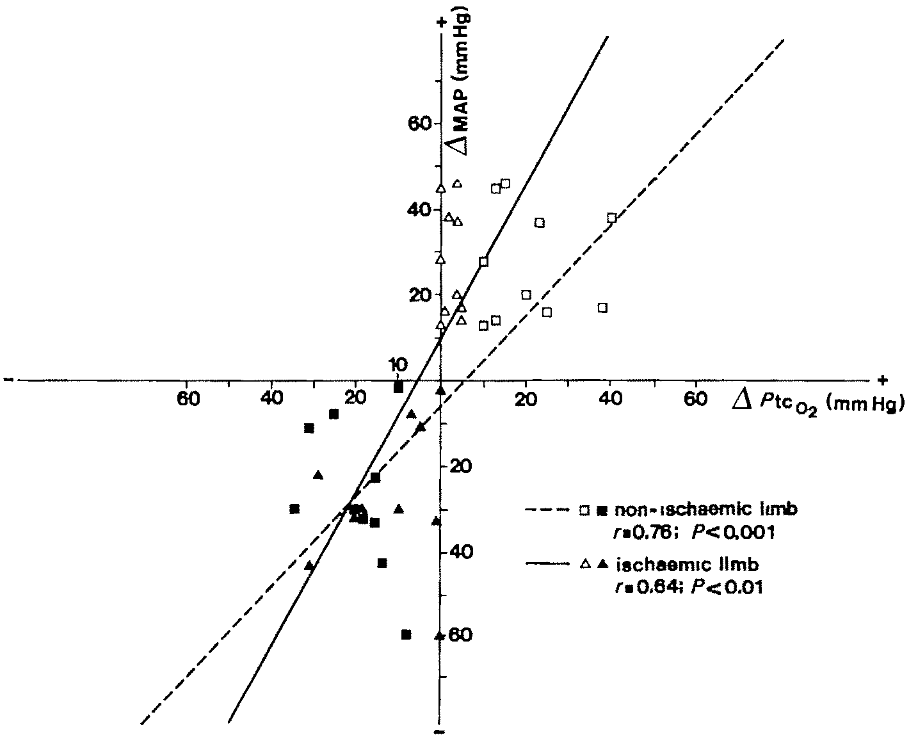

FIG. 1. Relationship between changes in mean arterial pressure (ΔMAP) and transcutaneous oxygen tension (ΔPtc_{O_2}) in ischaemic and non-ischaemic limbs after maximum extradural blockade (▲ = ischaemic; ■ = non-ischaemic) and after the administration of ephedrine (△ = ischaemic; □ = non-ischaemic) in 10 vascular patients.

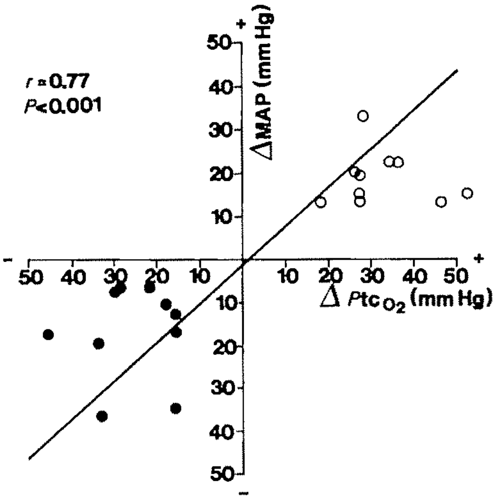

FIG. 2. Relationship between changes in mean arterial pressure (ΔMAP) and combined transcutaneous oxygen tension (ΔPtc_{O_2}) of the lower limbs after maximum extradural blockade (●) and after administration of ephedrine (○) in 10 urological patients.

flow to the skin (with a concomitant increase in skin temperature) (Mellander and Johansson, 1968; Herman, Dworecka and Wisham, 1970; Gillespie, 1973; Uhrenholdt, 1973). Skin capillary oxygen tension and saturation have been shown to increase following sympathetic denervation (Lofstrom and Zetterquist, 1967; Bridenbaugh, Moore and Bridenbaugh, 1971; Hatangdi and Boas, 1985).

In patients with peripheral vascular disease, the effects of sympathetic blockade are unpredictable, and published results of studies on skin blood flow after sympathectomy are conflicting (Uhrenholdt et al., 1971; Delaney and Scarpino, 1973; Morrice et al., 1975). Since accurate measurement of skin blood flow in the clinical situation is technically difficult, skin temperature is frequently used as an indicator of skin blood flow, on which it is largely dependent (Joly and Weil, 1969; Wright and Cousins, 1972). It has also been reported that variations of temperature following sympathectomy are related to arterial pressure at the ankle (Thulesius, Gjöres and Mandaus, 1973; Uhrenholdt, 1973).

In our study, we attempted to distinguish between the effects of extradural analgesia on ischaemic limbs in patients with unilateral vascular disease so that the unaffected limb could serve as a control. In addition, we had a further control group of patients (urological) without arteriosclerotic vascular disease. Although advanced arteriosclerotic vascular disease is often widespread, it may be more severe in one limb than the other. Thus, it is possible that, in our vascular patients, some degree of arteriosclerotic vascular disease may have been present in the "non-ischaemic limb". However the finding that Ptc_{O_2} in this limb (table II) was the same as that in the urological group (table III) suggests that the degree of arteriosclerotic disease in the non-ischaemic limb was minimum. In the non-ischaemic limb Ptc_{O_2} was higher (66.2 ± 5.5 mm Hg) than that of the ischaemic limb (32.7 ± 18.5 mm Hg). The clinical diagnosis of unilateral ischaemia was based on history, physical examination and haemodynamic measurements (Yao, 1970; Raines et al., 1976), supplemented by angiographic findings.

We found that the hypotension associated with maximum extradural blockade correlated significantly with the decrease in Ptc_{O_2}, indicating a decrease in blood flow. In the non-ischaemic limb, this reduction was unlikely to be of clinical significance, but in the ischaemic limb in which blood flow was already critical, a further decrease in blood flow could cause further deterioration in tissue oxygenation.

Cutaneous temperature increased significantly in the non-ischaemic limb after the extradural blockade, but did not change in the ischaemic limb. The finding of increased temperature, together with a decrease in Ptc_{O_2} (an indication of a decreased blood flow) would suggest that the increase in skin temperature after extradural blockade was the result of cutaneous vasodilatation and hyperaemia (Uhrenholdt et al., 1971). The difference between our findings and those reported by Wright and Cousins (1972) may be explained by differences in the magnitude of the decrease in MAP. In the vascular bed of an ischaemic limb, blood supply is reduced, transluminal pressure low and the vessels are maximally dilated because of the accumulation of vasodilator metabolites and loss of myogenic tone. Under these circumstances, sympathectomy may be unable to dilate the vessels of the ischaemic limb further, but may do so in other regions and induce a decrease in perfusion pressure and a reduction in blood flow to the ischaemic limb (Mellander and Johansson, 1968). Our finding supports the view that often sympathectomy does not benefit those limbs that most need an increase in blood flow (Froysaker, 1973; Uhrenholdt, 1973).

Previous studies (Modig, Malmberg and Karlstrom, 1980; Modig et al., 1983) have demonstrated that extradural analgesia increases blood flow to the large vessels of the lower limb, but appears to decrease local blood flow in the small vessels. This may explain the reduction in intraoperative blood loss during extradural analgesia.

Extradural blockade can affect the cutaneous circulation in several ways. It causes arteriolar vasodilatation, leading to a decrease in MAP and pulmonary artery pressure (Modig and Malmberg, 1975). Arteriovenous anastomoses in the skin are opened. The large blood flow through these anastomoses results in a steal of blood from the superficial cutaneous capillaries (Cronenwett et al., 1983), and both of these effects result in decreases in the blood flow to the skin and in Ptc_{O_2} (Davis and Greene, 1959).

The present study has demonstrated that extradural blockade decreased Ptc_{O_2} in limbs of both groups of patients. When ephedrine was given to increase the arterial pressure to preblockade values, Ptc_{O_2} increased. This finding is consistent with the previously reported results in animals (Tremper, Waxman and Shoemaker, 1979) and man (Tremper and Shoemaker, 1981) that Ptc_{O_2} increases with an increase in cardiac output. It has been shown that, in the presence of either subarachnoid (Ward et al., 1966) or extradural blockade (Engberg and Wiklund, 1978), the administration of ephedrine causes an increase in MAP but has minimal effect on peripheral vascular resistance in the area of the block. The increase in arterial pressure with induced vasodilatation in the lower limbs may beneficially increase flow to the legs and thus Ptc_{O_2} (Hatangdi and Boas, 1985).

In conclusion, sympathectomy, if it is to be of value in patients with ischaemic limbs, should be combined with measures designed to prevent any decrease in mean arterial pressure.

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FACTORS AFFECTING DELIVERY OF DRUG THROUGH EXTENSION TUBING

P. HUTTON AND E. A. THORNBERRY

SUMMARY

A theoretical laminar flow model of drug delivery via extension sets (1250 mm long) was developed and tested experimentally by tracer studies. Despite discrepancies between theory and experiment (which are discussed in the text), when the infusion was allowed to run normally it was confirmed that there was a hyperbolic relationship between the flow rate of the infusion and the time of delivery of a given percentage of the injected drug. Even with the drip chamber (15 drops ml^{-1}) running as a continuous stream, it can take up to almost 3 min for 90% of a 1-ml or 3-ml injection to enter the patient's vein. An alternative method of flushing the drug in with a syringe of saline produced a non-laminar flow regimen which was more efficient in terms of both the volume and the time required for a given percentage drug delivery.

During anaesthesia, drugs are frequently administered i.v. via the self-sealing rubber injection site at the patient end of an i.v. administration set. If, during surgery, the position of the i.v. cannula is inaccessible, the injection site can be moved to a more convenient place by the use of extension tubing. When this was done during clinical investigations involving neostigmine, it was noted that, on several occasions following its injection, there was an unexpected delay of over 6 min before the effect of neostigmine was seen. Therefore it was decided to investigate the delivery time of drugs injected via extension tubing and to see how this varied with the rate of the i.v. infusion.

MATERIALS AND METHODS

Experimental investigation

A 1-litre container of physiological saline was connected to a cannula (Abbocath 16-gauge) via a standard i.v. fluid administration set (Avon Medicals type A100) and extension tubing (Avon Medicals type A60, length 1250 mm, volume 15 ml) as shown in figure 1. The infusion rate was controlled over a wide range by raising or lowering the bag of saline and adjusting a gate clamp on the tubing of the giving set. Injections were made with physiological saline coloured with bromophenol blue, the concentration of which was measured by absorption at 590 nm on a u.v. spectrophotometer (Cecil Instruments type CE595).

The following procedure was used to establish the delivery time of a given fraction of the injectate. First, the nominal infusion rate was set by adjusting the gate clamp on the tubing (fig. 1). The tubing of the giving set was then compressed with forceps immediately below the drip chamber to stop the flow. The injection of dye was then made very slowly in order not to induce turbulent mixing (fig. 1). At the end of the injection the dye occupied that portion of the extension set immediately adjacent to the injection site, and the volume of saline equal to the volume of dye injected—which was delivered from the cannula—was discarded. Finally, the tube was unclamped and the saline discharging from the Abbocath was collected at predetermined time intervals in a series of beakers. The volume of the solution and the concentration of bromophenol blue in each was measured. Knowing the initial volume injected and the concentration of bromophenol blue enabled the proportion delivered through the cannula into each beaker to be calculated. The overall coefficient of variation of the assay using

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P. HUTTON, B.SC., PH.D., M.B., CH.B., F.F.A.R.C.S.; Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW. E. A. THORNBERRY, M.B., B.S., F.F.A.R.C.S.; Shackleton Department of Anaesthesia, Southampton General Hospital, Southampton.

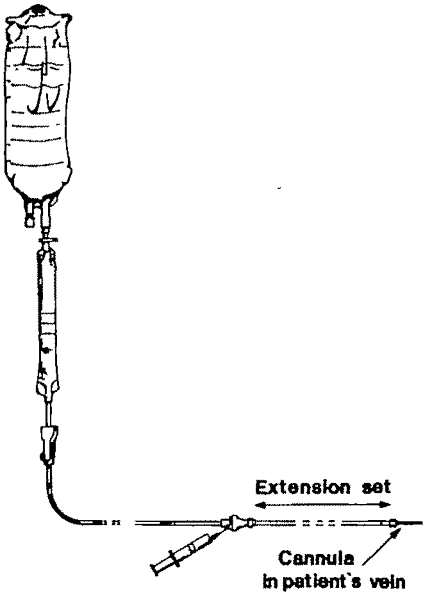

FIG. 1. Diagrammatic representation of i.v. fluid administration set and extension tubing.

this method was below 3%. Data were obtained with injection volumes of 1 ml and 3 ml at infusion rates of from 2 ml min^{-1} to 100 ml min^{-1}.

However, in practice, drugs are not always transmitted to the patient by allowing the drip to run as described above; sometimes they are flushed in from the injection site. Consequently, injections of 1 ml and 3 ml of coloured saline were made as described above with the tubing clamped and, while it remained clamped, further boluses of up to 30 ml of clear saline were injected at approximately 2 ml s^{-1}. The fluid delivered from the cannula following each bolus was collected in a beaker, and the proportion of the original injectate delivered was measured by the methods detailed earlier.

Theoretical analysis

The usefulness of dye and temperature dilution techniques for measuring flow has, in both industry and physiology, produced a literature describing the behaviour of the injectate following mixing with the main flow (Taylor, 1953; Bate et al., 1969; Bate, Rowlands and Sirs, 1973; Lane and Sirs, 1974a, b; Patel and Sirs, 1983).

The partial differential equation describing the concentration (c), of the indicator as a function of time (t), axial distance (x), and radial distance (r), under conditions of Poiseuille flow in a straight tube of radius r_0 is (Taylor, 1953; Bate et al., 1969; Bate, Rowlands and Sirs, 1973):

$$\frac{\partial c}{\partial t} = D\left[\frac{\partial^2 c}{\partial r^2}+\frac{1}{r}\frac{\partial c}{\partial r}+\frac{\partial^2 c}{\partial x^2}\right]-2\bar{u}\left[1-\frac{r^2}{r_0^2}\right]\frac{\partial c}{\partial x}$$

where $\bar{u}$ is the mean axial velocity of the mainstream fluid and D is the diffusion coefficient of the indicator. However, all solutions have assumed the volume of the indicator solution to be small, and have concentrated on the prediction of the average cross-sectional value of the indicator concentration. There is, to our knowledge, no exact solution readily available to calculate the proportion of injectate which has passed a fixed point downstream of the injection site after a given time.

In order to construct an adequate theoretical model it is first necessary to ascertain the flow regimen in the tubing between the giving set and the patient. The highest flow rate used in our experiments when the drip chamber was running freely was approximately 100 ml min^{-1}. With the dimensions of the tubing given above and taking the kinematic viscosity of saline (ν) to be 1.2×10^{-6} m^2 s^{-1} (Sabersky and Acosta, 1966a), this gives a Reynolds number ($Re = [2\bar{u}r_0]/\nu$) of 450. This is well within the laminar range, the lower limit for turbulence being a Reynolds number of approximately 2000. It is, therefore, appropriate to adopt a laminar flow model for theoretical analysis.

However, the low Reynolds number, whilst confirming laminar flow, does not imply necessarily that the velocity profile must be parabolic. At the entrance to any tube (which in this case is at the bottom of the drip chamber) the velocity profile, although laminar, is quite square and it takes time for the frictional drag of the wall of the tube and that between the fluid layers to establish the parabolic shape. This effect is shown diagrammatically in figure 2 and the linear distance required to accomplish a parabolic velocity profile is known as the entry length (Xe) and is given by (Prandtl and Tietjens, 1957):

$$X\mathrm{e} = 0.13 r_0 Re$$

For the giving set used and a Reynolds number of 450, Xe = 115 mm. This implies that, 115 mm from the drip chamber, a parabolic velocity profile will have developed fully. As the tubing supplied with the giving set is 1530 cm long, this fully developed profile will be present at the entrance to the extension tubing (fig. 1) where the injection is

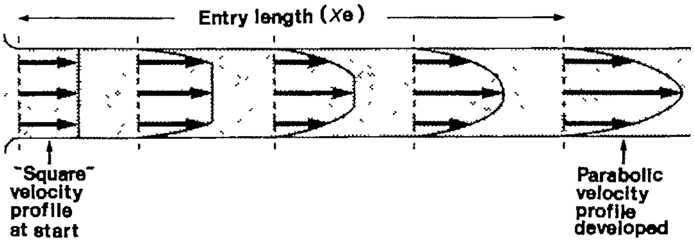
Entry length (Xe)
"Square" velocity profile at start
Parabolic velocity profile developed

FIG. 2. The development of a parabolic velocity profile at the entrance to a pipe of circular cross section.

made. The length of the giving set tubing being more than 10 times the theoretical entry length further ensures that any disturbances to the flow regimen subsequently produced by the compression clamp below the drip chamber (fig. 1) will also be removed well before the entrance to the extension set. Consequently, the assumption of a fully developed parabolic velocity profile in the extension set tubing as the basis for the analysis shown below is justified on theoretical grounds with the infusion rates used in this study.

To obtain a theoretical solution, the model shown in figure 3 was analysed under the conditions of fully developed Poiseuille flow with no diffusion. Figure 3A represents the situation with the flow arrested immediately after injection (time $t = 0$). The length of the extension tube is L, the distance S being occupied by the injectate volume $V\mathrm{i}$. Once the flow (Q) is allowed to start, each of the leading and trailing surfaces of the injectate moves forward with a parabolic velocity profile. This, after time t, deforms and transports the initial cylinder of injectate to the shape and position shown diagrammatically in figure 3B, the volume of injectate entering the patient being given by $V\mathrm{d}$.

It is shown in Appendix 2 that:

$$V\mathrm{d} = 0 \text{ until } t = \frac{L-S}{2\bar{u}} \tag{1}$$

$$V\mathrm{d} = \left[Qt - \pi(L-S)\,r_0^2 + \frac{\frac{1}{4}\pi^2(L-S)^2 r_0^4}{Qt}\right]$$
$$\text{when } \frac{L-S}{2\bar{u}} < t < \frac{L}{2\bar{u}} \tag{2}$$

$$V\mathrm{d} = V\mathrm{i} - \left[\frac{1}{Qt}\left(\frac{\pi r_0^2 L V\mathrm{i}}{2} - \frac{V\mathrm{i}^2}{4}\right)\right] \text{ when } t > \frac{L}{2\bar{u}} \tag{3}$$

It can be seen from equation (3) that, because t appears in the denominator, it theoretically takes an infinite time for the whole of the injected dye to be delivered through the cannula. However, if it is required to find the time taken for say 90% of the injected value $V\mathrm{i}$ to be delivered, then this can be done by putting $V\mathrm{d} = 0.9\ V\mathrm{i}$ in equation (3) and solving for t.

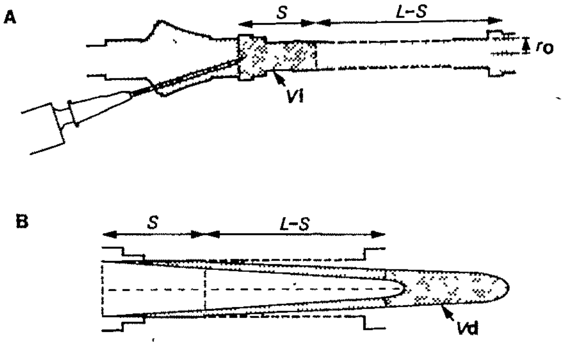

FIG. 3. Diagrammatic representation of position of dye immediately after injection (A), and later as it enters the patient (B).

RESULTS

The results of measuring experimentally the delivery of dye when the drip set was allowed to run following the injection are shown in figure 4. For clarity, figure 4 shows the percentage delivery with time for a 1-ml injection at only three flow rates. Curves of this type were in fact determined at nine flow rates for both the 1-ml and 3-ml injection volumes. For comparison, the theoretical delivery times as determined by equations (2) and (3) (above) are also shown.

Because, theoretically, it takes an infinite time for the total dose of injected dye to enter the patient, it was decided to examine the time necessary for 90% to be delivered. The times for

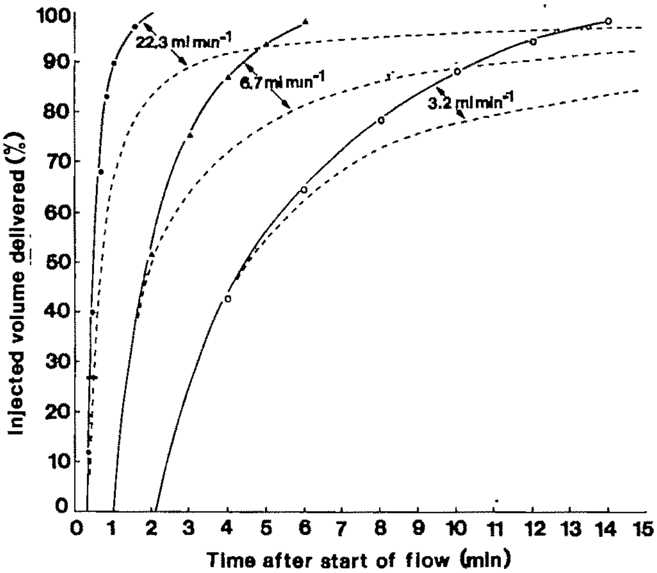

FIG. 4. Comparison between theoretical and observed times of delivery of 1.0 ml of injected dye. The flow rates are marked. The theoretical delivery is represented by the dotted lines and the experimental delivery by the solid lines.

90% delivery of the 1-ml and 3-ml injected volumes at different flow rates were determined from the interpolation of percentage delivery curves as shown in figure 4. These results are shown in figure 5. Because the differences between the 1-ml and 3-ml results were so small, a single curve was drawn through the points for convenience. For comparison, the curves for the theoretical prediction of 90% delivery time calculated from equation (3) (above) are also plotted in figure 5.

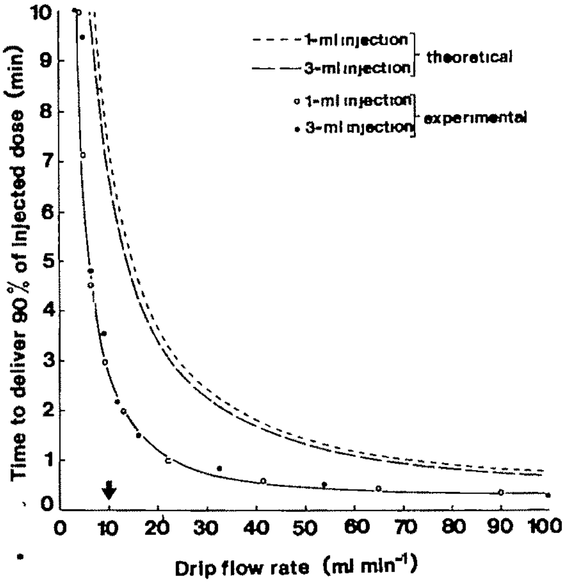

FIG. 5. The effect of drip flow rate on the time required to deliver 90% of 1-ml and 3-ml injected volumes determined theoretically and experimentally. At approximately 10 ml min^{-1} (arrowed) the individual drops of a standard giving set (15 drops ml^{-1}) become a steady stream.

The percentage deliveries of 1-ml and 3-ml volumes of dye resulting from rapid flushing with different volumes of 0.9% saline are shown in figure 6.

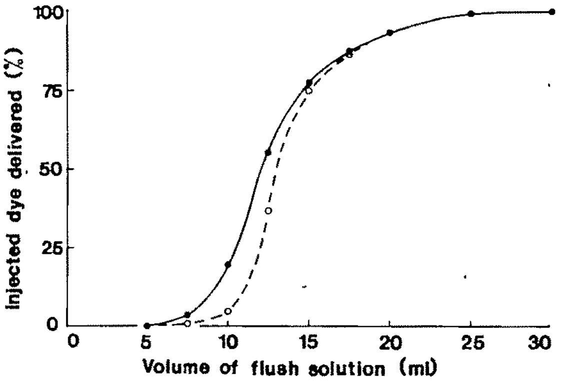

FIG. 6. The percentage delivery of injected dye (○ = 1 ml; ● = 3 ml) following flushing with different volumes of flush solution at 2 ml s^{-1}.

DISCUSSION

With the infusion running in the normal manner to flush in the dye (figs 4 and 5), although the trend in theoretical and experimental results is similar, there is an obvious numerical discrepancy between them. Considering figure 4, there is an initial time lag equal to $(L-S)/2\bar{u}$ (see Appendix 2) before any dye delivery occurs at all. This corresponds to the time it takes for the fastest moving particles on the axis of the stream to traverse the distance $(L-S)$. It can also be seen that the theoretical and experimental times to approximately 50 % delivery are in good agreement but that, after this, the disparity increases continuously. Were a graph of 50 % and not 90 % delivery plotted out on the same format as figure 5, the agreement between theory and practice would be excellent. We chose 90 % because it is assumed that the whole of the given dose is intended to reach the patient.

The fact that the error between the theoretical and practical results grows rapidly above 50 % delivery means that the error is generated when the transport of dye depends increasingly upon the "tail" of the parabolic transport kinetics (Appendix 2). There are several factors which would contribute to increasing the delivery of dye during this phase. As the flow moves from the vertically downwards direction (below the giving set drip chamber) to the horizontal direction (fig. 1), it necessarily induces secondary currents moving circumferentially. This problem has been studied in detail by Dean (1927) and McConalogue and Srivastava (1968). In summary, their results demonstrate that, fluid having negotiated the bend, there is a superimposed circumferential velocity (fig. 7) which causes the individual fluid elements to move with a helical path. This has the greatest effect on those regions near the wall which theoretically take the longest to get to the delivery cannula. The dye in these slow velocity regions close to the wall will be transported into a faster flowing central stream.

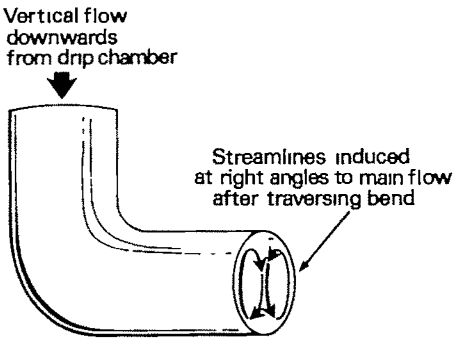
Vertical flow downwards from drip chamber
Streamlines induced at right angles to main flow after traversing bend

FIG. 7. Circumferential velocities induced by flow traversing a bend.

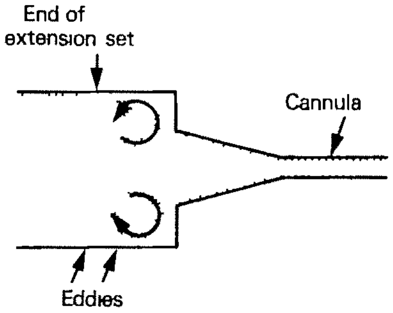

FIG. 8. Eddies induced at the junction of the extension set and the i.v. cannula.

Although only a 90° bend in the tubing (fig. 1) was used experimentally and is shown in figure 7, in clinical practice the tubing may either slope gently downwards or possess an even more convoluted form. In general, the greater the angle of curvature or the number of loops in the tubing, the greater the magnitude of the secondary flows.

Streamline mixing is promoted also as the fluid enters the cannula because of the eddies occurring when there is a sudden change in diameter (fig. 8). In addition, the junction between the giving set and extension tubing will produce a minor disturbance to the parabolic velocity profile. All these perturbations have the greatest effect on those components of the dye layers nearest the wall.

Another factor which has been considered previously by Taylor (1953) and Bate, Rowlands and Sirs (1973) during dye dilution experiments is the diffusion of tracer ions across the cross section where the mainstream fluid forms an interface with the dye. The rate of diffusion obviously depends upon the concentration gradient, the relative molecular weights and the area of the interface. Bate, Rowlands and Sirs (1973) demonstrated that the influence of diffusion in a laminar flow model has a much greater effect on the trailing than on the leading edge of the dye–fluid interface. This can be appreciated intuitively because, not only is there more time for diffusion to occur before the slow moving portions of the stream reach the cannula, but also the net diffusion of tracer is predominantly radially inwards, that is, into a more rapidly moving stream.

In summary, therefore, the theoretical model described in Appendix 2 calculates the slowest possible delivery time for drugs. It is in error because of swirl from secondary flows, eddies and molecular diffusion, all of which transport dye from low to higher velocity streamlines. These effects all have a proportionately much greater influence on the tail rather than the front of the dye–saline interface. Accordingly (fig. 4), the theoretical solution calculates the percentage delivery times accurately to up to approximately 50% delivery, after which the errors become appreciable, producing an inaccuracy of over 100% in the time required for 90% delivery.

At a given percentage drug delivery, the relationship between Vi, Vd, Q and t is that described by equations (2) and (3) above. If Vi and Vd/Vi are specified (the injected volume and the percentage delivery of that injected volume), then for given extension tubing equation (3) reduces to the form:

$$\text{time for given percentage delivery} = \left[\frac{\text{constant}}{\text{flow rate}}\right] \tag{4}$$

This is a hyperbolic relationship and the two theoretical curves shown in figure 5 are rectangular hyperbolae, the small difference between them being the result of Vi being taken as 1 ml and 3 ml. A corollary of equation (4) is that the same volume of fluid must run into the patient to deliver a given percentage of the injected drug, *irrespective of the flow rate.*

When the experimental results were plotted in figure 5, it was found that the experimental points still fitted very closely to a rectangular hyperbola with the equation:

$$\text{Flow rate (ml min}^{-1}) \times \text{time to } 90\% \text{ delivery (min)} = 28.6 \text{ ml}$$

This means that, at whatever flow rate the drip is set, 28.6 ml of saline must leave the 1-litre bag for 90% of 1-ml and 3-ml injections to reach the patient. In practice, it may be easier to observe this volume leave the bag or burette rather than time a period for an assumed flow rate. This has special relevance when the infusion is running as a continuous stream and the flow rate is difficult to judge.

Using the normal drip set (15 drops ml^{-1}) at or above approximately 10 ml min^{-1}, the stream in the drip chamber becomes continuous. This rate is marked on figure 5, where it can be seen that there is a theoretical 90% delivery time of 7 min and an actual 90% delivery time of 2.8 min. Although the theoretical model over estimates the true 90% delivery time, almost 3 min is probably a much longer time than that which one would intuitively expect for 90% drug delivery with a drip running in a continuous stream. This has obvious implications for drugs which one wants to act immediately or those of which the time of administration is to be recorded accurately. Furthermore, if the delivery time is not appreciated, it is easy to inject an unnecessary second dose of drug before the first has reached the patient and produced an effect. It can also be seen from figure 5 that the 90% delivery time increases rapidly as the drip flow rate decreases. For example at 4 ml min^{-1} (1 drop s^{-1}) the measured 90% delivery time for the 1-ml and 3-ml injections was 8 min.

A corollary of the above discussion is that, if one wants to give a drug slowly, then it is easy to do so by injecting it to the delivery system some distance from the patient and then allowing the drip to run at the appropriate rate. The parabolic dyefront which develops subsequently prevents a sudden step input of drug to the patient.

The kinetics of drug delivery following flushing with saline at approximately 2 ml s^{-1} are shown in figure 6. The Reynolds number at this flush rate based on the diameter of the tubing and the data given above is 540, a number well within the laminar range. The flow down the extension tubing was, however, visibly not laminar over the first 50 cm. The syringe used for the saline flush was fitted with a 21-gauge needle (internal diameter = 0.4 mm) and, at 2 ml s^{-1}, the exit velocity and Reynolds number of the jet emerging from the tip were 15.9 m s^{-1} and 5300, respectively; that is, well into the turbulent region.

During flushing, the momentum of the jet could be seen to project the flush solution, and hence the dye with which it mixed, for almost half the length of the extension tubing before being suppressed by viscous forces. Simultaneously, the turbulence created by the jet promoted mixing across the cross section and a longitudinal plug flow regimen with a square velocity profile. Figure 6 shows that 18 ml of flush injected at 2 ml s^{-1} will deliver 90% of a 1-ml or 3-ml injection and that this delivery is complete within 9 s.

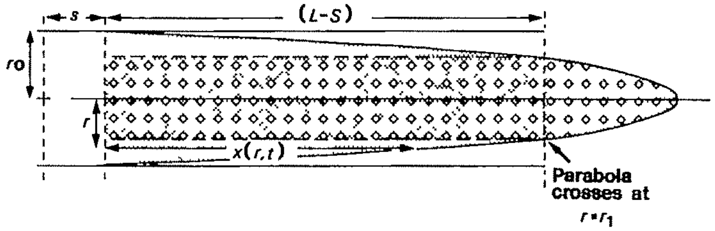

FIG. 9. Diagrammatic representation of a parabolic dyefront. The trailing dye boundary is omitted for clarity.

CONCLUSION

When injections are made via an extension set with the drip chamber allowed to run in the normal manner, a laminar flow model provides a good qualitative description of drug delivery. After 50% of the injected volume has been delivered the theoretical model does, however, for reasons discussed in the text, progressively overestimate the time required for a given percentage drug delivery. Despite this, at up to 90% delivery, there is an experimentally confirmed hyperbolic relationship between drip flow rate and the time required for a given percentage delivery of injected drug. This implies that, whatever the drip rate, the same volume of saline must leave the reservoir bag to deliver the same fraction of injected drug.

The alternative method of flushing the drug in with a syringe of saline produces a more turbulent flow regimen which is more efficient in both the time and volume of saline required to deliver a given fraction of injected drug.

APPENDIX 1

LIST OF SYMBOLS

c = Concentration of indicator
L = Length of extension tubing
Q = Volume flow rate
Re = Reynolds number = $(2\bar{u}r_0)/\nu$
r = Radial distance
r_0 = Internal radius of tube
r_1 = Radius of dye front as it crosses the end of the extension tubing at time t
S = Length of extension tubing occupied by injected dye
t = Time
$\bar{u}$ = Mean axial velocity
$u(r)$ = Axial velocity at radius r
Vi = Volume of dye injected
Vd = Volume of dye delivered into patient
ν = Kinematic viscosity
x = Axial distance down tubing
$x(r,t)$ = Axial distance moved by the dye at radius r at time t
Xe = Entry length

APPENDIX 2

THEORETICAL ANALYSIS OF DYE TRANSPORT

There are three phases of drug delivery to be considered:

(a) Assuming a parabolic velocity profile, the axial velocity is twice the mean velocity of the fluid (Sabersky and Acosta, 1966b). Therefore no dye is delivered at all until time t such that $t > (L-S)/(2\bar{u})$.

(b) Once t is greater than $(L-S)/2\bar{u}$, the leading edge of the dye stream begins to cross the end of the extension set and injectate begins to be delivered through the cannula. The situation at time t is redrawn in figure 9 and the trailing dye boundary (which for the moment is assumed not to have reached the end of the extension set) is omitted for clarity.

Initially the injectate has a plane dyefront at distance S (fig. 3A) and once the flow is started the velocity $u(r)$ at radius r is described by (Sabersky and Acosta, 1966b):

$$u(r) = \frac{2Q(r_0^2-r^2)}{\pi r_0^4} \qquad \text{(i)}$$

After a time t, the dyefront will occupy a profile (fig. 9) described by:

$$x(r,t) = \frac{2Qt(r_0^2-r^2)}{\pi r_0^4} \qquad \text{(ii)}$$

The value of r at which this profile crosses the end of the extension tubing (r_1, fig. 9) at time t will be given by that radius at which $u = (L-S)/t$.

Putting $[(L-S)/t = u]$ into (i) gives:

$$r_1 = \sqrt{\left[r_0^2 - \frac{\pi(L-S)r_0^4}{2Qt}\right]} \qquad \text{(iii)}$$

Considering figure 9, it can be seen that the volume of injectate delivered is equal to the volume shaded by circles minus the volume shaded by the heavy stippling. The shaded volume occupied by circles equals:

$$\int_0^{r_1} (2\pi r dr x(r,t))$$

and, by substitution from (ii) for $x(r,t)$ and integrating, this becomes:

$$4Qt[\tfrac{1}{2}(r_1/r_0)^2 - \tfrac{1}{4}(r_1/r_0)^4] \qquad \text{(iv)}$$

The shaded volume occupied by the heavy stippling equals:

$$(\pi r_1^2(L-S)) \qquad \text{(v)}$$

The volume delivered to the patient is therefore given by equation (iv) minus equation (v):

$$Vd = 4Qt[\tfrac{1}{2}(r_1/r_0)^2 - \tfrac{1}{4}(r_1/r_0)^4] - \pi r_1^2(L-S)$$

and, substituting r_1 from (iii) results in:

$$Vd = Qt - \pi(L-S)\,r_0^2 + \frac{\pi^2(L-S)^2 r_0^4}{4Qt} \qquad \text{(vi)}$$

(c) At time $t > L/2\bar{u}$, the axial streamline of the trailing dye boundary will cross the end of the extension tubing and the volume of injectate delivered to the patient will be bounded by two paraboloids of revolution, as shown in figure 3B.

The volume of the smaller paraboloid, which consists of dye-free fluid can be deduced in a manner exactly analogous to the method used in (b) above to be given by:

$$Qt - \pi L r_0^2 + \frac{\pi^2 L^2 r_0^4}{4Qt}. \qquad \text{(vii)}$$

The volume delivered to the patient (Vd) is then given by equation (vi) minus equation (vii). Substituting in the volume of the injectate, Vi, for $\pi r_0^2 s$ results in:

$$Vd = Vi - \left[\frac{1}{2Qt}(\pi r_0^2 L Vi - \tfrac{1}{2}Vi^2)\right]. \qquad \text{(viii)}$$

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INTERACTION OF CYCLOSPORIN AND ITS SOLVENT, CREMOPHOR, WITH ATRACURIUM AND VECURONIUM

Studies in the Cat

L. GRAMSTAD, J. A. GJERLØW, E. S. HYSING AND H. E. RUGSTAD

SUMMARY

Interactions between Sandimmun (formulated as cyclosporin (CyA) in Cremophor and ethanol) and atracurium or vecuronium were investigated in anaesthetized cats. During stable 50% blockade and with a constant rate of infusion of the neuromuscular blocking drugs, Sandimmun 0.8 mg kg^{-1} or an equivalent amount of its solvent moiety was injected over 5 min. Sandimmun potentiated the blockade induced by vecuronium (median infusion rate 110 μg kg^{-1} h^{-1}) from 50.7% before injection to maximum 95.2% 17.3 min after injection (median values), whereas the median blockade in cats receiving atracurium (median 250 μg kg^{-1} h^{-1}) increased from 51.3% to 72.4% after 32.9 min. At 45 min after the injection the median blockades were 93.1% and 69.8%, respectively. In cats receiving vecuronium (median 104 μg kg^{-1} h^{-1}) the solvent produced an increase in effect of from 51.1% to maximum 78.0% blockade after 5.4 min and 61.5% after 45 min (median values). Interaction with solvent was negligible in cats receiving atracurium. We attribute the effect of the solvent to the Cremophor component. The mechanism of the interaction related to the cyclosporin is unknown.

The pharmacokinetics of the neuromuscular blocking agents atracurium and vecuronium do not differ significantly between patients with normal renal function and those in renal failure (Fahey et al., 1981; Fahey et al., 1984). As a result, both drugs appear suitable for use during anaesthesia in patients suffering from renal failure. However, in patients receiving kidney allografts, the immunosuppressive drug cyclosporin (Sandimmun, Sandoz) may be used to prevent the rejection of the transplanted organ. Cyclosporin is often administered as an i.v. infusion during renal transplantation, concomitantly with the anaesthetic and neuromuscular blocking agents.

Preliminary investigations in cats indicated that small clinical doses of cyclosporin potentiated the neuromuscular blocking action of vecuronium; the interaction with atracurium was less pronounced. A randomized study in cats has been designed to investigate in more detail the action of cyclosporin, and its solvent, on neuromuscular blockade induced by atracurium or vecuronium.

MATERIALS AND METHODS

Anaesthesia and surgical preparation

Twenty-four cats bred for biomedical research (Institute of Physiology, University of Gothenburg) were used. They were of either sex, aged 10.6–12.4 months and weighed between 2.15 and 4.65 kg.

Anaesthesia was induced with pentobarbitone 20–30 mg kg^{-1} i.p. with supplementary i.v. increments as required, and maintained with an i.v. infusion of the barbiturate at a rate of 5–7 mg kg^{-1} h^{-1} using a 0.5% solution in 3.5% glucose with 0.3% sodium chloride. Following tracheal intubation, mechanical ventilation was instituted at a rate of 27 b.p.m. with 50% oxygen in air using an Ideal Pump 16/24 ventilator. Tidal volume was adjusted to maintain arterial pH between 7.30 and 7.50, and sodium bicarbonate was given to correct acidosis before neuromuscular blockade was induced. Arterial blood-gas tensions,

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L. GRAMSTAD,* M.D.; J. A. GJERLØW, M.D.; E. S. HYSING, M.D. (Department of Anaesthesia and Institute of Surgical Research); H. E. RUGSTAD, M.D. (Department of Clinical Pharmacology); Rikshospitalet, University Hospital, N-0027 Oslo 1, Norway.

*Present address: Apothekernes Laboratorium A.S, Harbitzalleen 3, N-0275 Oslo 2, Norway.

pH and base excess were determined (Radiometer ABL-1, adjusted to 37 °C). A circulating water blanket was used to maintain rectal temperature at 38–39 °C (Digimed H10 thermometer). A cannula was placed in a carotid artery for blood sampling and to allow monitoring of arterial pressure. The ECG was registered. An external jugular vein was cannulated to permit the infusion of the neuromuscular blocking drug. A third vein was cannulated for the infusion of a solution of 3.5% glucose with 0.3% sodium chloride. Total fluid load was adjusted to 7–8 ml kg^{-1} h^{-1}.

The tendon of the right anterior tibialis muscle (the left muscle in one cat) was freed, and separated from its insertion by cutting off a small piece of the bony attachment. A short braided silk thread was tied around the tendon and connected to a Statham UC3 transducer equipped with a UL4-10 load cell adapted for tension force. The output of the transducer was registered on a Graphtec WR3101 recorder using a Hewlett–Packard 8805C amplifier. The resting tension of the muscle was maintained at 50 g. A Digimed F3 temperature probe was placed subcutaneously on the muscle belly. Radiation from an electric lamp was used when required to maintain muscle surface temperature at 36–37 °C.

The sciatic nerve was exposed in the thigh, and cut proximally. The tibial nerve was sectioned near the popliteal space. A shielded bipolar platinum electrode was placed on the peroneal nerve, and supramaximal stimuli were applied at 0.1 Hz (Myotest MKII nerve stimulator).

The hind limb was fixed securely to a rigid frame by pointed clamps at the knee and at the ankle. Wound edges were sutured.

Drugs

Atracurium and vecuronium were diluted in 0.9% saline at 4 °C and room temperature, respectively, before infusion. The concentrations were atracurium 0.2 mg ml^{-1} and vecuronium 0.08 mg ml^{-1}. Sandimmun 1 ml (cyclosporin 50 mg in 94% ethanol 0.278 g and Cremophor EL 0.650 g) was diluted to 10 ml by the addition of physiological saline. The mixture of 94% ethanol 0.278 g and Cremophor EL (BASF, Ludwigshafen, GFR) 0.650 g makes 0.96 ml of solution. To this amount of solvent, 0.9% saline 9.04 ml was added, to make 10 ml.

Procedure

The 24 cats were allocated randomly to three equal groups. Groups 1 and 2 received vecuronium and, subsequently, Sandimmun (group 1) or solvent (group 2). Group 3 received atracurium and, subsequently, Sandimmun. This design was chosen because Sandimmun potentiated vecuronium more than atracurium in our pilot study. However, to get an indication of differential interactive effects of Sandimmun and its cremophor moiety with atracurium in group 3, we tested two subgroups of three and four cats with drug or solvent, respectively, later in the investigation. The nature of the Sandimmun interaction was investigated further by giving this drug to a subgroup of five cats in group 2 after the recovery of normal neuromuscular function.

In all cats the control twitch height was allowed to stabilize for at least 27 min, while rectal and muscle surface temperatures were adjusted, if required, before neuromuscular blockade was induced. The neuromuscular blocking agent was given as a continuous infusion using a Hoechst PP50 infusion pump. After an initial fast rate of infusion, the rate was titrated to produce constant 50% depression of the control twitch response. When the infusion of the neuromuscular blocker had lasted for 60 min, the rate of infusion was maintained steady, and the drug requirement as well as the twitch response registered. After a subsequent 15-min period the twitch response was measured again. With the rate of infusion stable, Sandimmun or solvent were now given over 5 min, and the catheter flushed by the infusion of 3.5% glucose with 0.3% saline. The dose of Sandimmun given to groups 1 and 3 equalled cyclosporin 0.8 mg kg^{-1}. Group 2 received a dose of solvent equivalent to that contained in the amount of Sandimmun received by groups 1 and 3. The onset time (from the completion of the injection until maximum neuromuscular blockade) was noted, and its value registered. Forty-five minutes after completion of the injection of the interacting agent, the degree of neuromuscular blockade was measured again. The infusion was then discontinued in groups 1 and 2, and the maximum recovery of the twitch response was recorded.

Forty-five minutes after the completion of the injection of Sandimmun, animals in group 3 (atracurium) received either a further dose of Sandimmun ($n = 3$) or an equivalent dose of the solvent ($n = 4$), both agents being injected over 5 min. The maximum change in twitch height was observed for 20–30 min. The infusion was then discontinued, and maximum recovery of twitch force recorded. The former subgroup included only three cats because the threshold for supramaximal stimulation of the nerve was increasing in one cat. Therefore, instead of the intended second dose of Sandimmun being administered, the infusion of atracurium was discontinued and the maximum degree of recovery was registered.

In group 2, which received only the solvent, recovery was allowed to continue in five cats until the twitch response was apparently stable. Sandimmun, equivalent to cyclosporin 1.6 mg kg^{-1}, was then given i.v. over 5 min, and the twitch response recorded for a further 15 min.

Statistics

Analyses of the data were performed using the Statistical Analysis System (SAS) on an IBM 4341 computer. Depression of twitch height was analysed statistically in probit-transformed values (Finney, 1952), because log–probit transformation yields a linear dose–response relationship for neuromuscular blocking drugs in the cat (Ginsburg, Kitz and Savarese, 1971). A preliminary assessment of our data using a goodness-of-fit test (Shapiro and Wilk, 1965) showed that, in some of the variables, approximation by a Laplace–Gaussian distribution was impossible. Therefore, we used only non-parametric analyses. A Wilcoxon's rank sum test was used for two-sample comparisons. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The three groups of animals did not differ with respect to age, weight and sex distribution (table I). There were no major differences between the groups in the physiological measurements at the time of the measurement of control twitch height and following 60 min of neuromuscular blockade (table II).

Constant-rate infusions

Approximately stable infusion–response conditions were obtained in all cats before the change in response during the 15-min period of maintained fixed-rate infusion was assessed. The responses before and after this time interval are given in table III. The individual changes (in % of control twitch height) from start to end of this 15-min period were (median with total range, in absolute values): 2 (0–4) in group 1, 2 (0–4) in group 2, and 2 (1–5) in group 3. The constant infusion rates of the neuromuscular blocking drugs were (in μg kg^{-1} h^{-1}, given as median with total range):

TABLE I. *Characteristics of the three groups of cats. Values are median and total range*

Group	Neuromuscular blocker	Interacting agent	*n*	Age (months)	Weight (kg)	Sex (m/f)
1	Vecuronium	Sandimmun	8	11.8 (10.8–12.2)	3.4 (2.15–3.7)	1/7
2	Vecuronium	Solvent	8	11.4 (11.0–11.9)	3.1 (2.4–4.65)	2/6
3	Atracurium	Sandimmun	8	11.1 (10.6–12.4)	2.85 (2.5–3.95)	1/7

TABLE II. *Temperatures at control twitch height, and temperatures and arterial blood-gas tensions and acid–base status once a constant-rate infusion had been established. The latter temperatures were registered at the time of maximum interaction, while the quoted blood biochemistry refers to the first sample taken after 60 min of blockade. Values are median and total range. BE = base excess*

	Rectal temperature (°C)		Muscle surface temperature (°C)		Arterial blood-gas tensions and acid–base balance			
Group	Control	Interaction	Control	Interaction	P_{O_2} (kPa)	P_{CO_2} (kPa)	pH	BE (mmol $litre^{-1}$)
1	38.2 (37.8–39.0)	38.6 (38.4–38.8)	36.4 (36.2–36.6)	36.6 (36.1–37.0)	34.5 (31.7–38.7)	4.6 (3.6–5.7)	7.43 (7.29–7.49)	−1.7 (−6.0–3.9)
2	38.9 (38.0–39.0)	38.6 (38.4–38.7)	36.7 (36.1–36.9)	36.6 (36.4–36.7)	34.6 (31.3–37.4)	4.4 (3.7–5.2)	7.42 (7.39–7.47)	−2.0 (−4.0–−0.4)
3	38.7 (38.0–39.0)	38.7 (38.5–38.9)	36.4 (35.6–36.6)	36.5 (36.4–36.9)	32.3 (26.2–34.7)	4.5 (3.9–6.8)	7.42 (7.28–7.50)	−2.8 (−4.5–0.6)

TABLE III. *Twitch depression during constant-rate infusion at 60 and 75 min of blockade. The augmentation of neuromuscular blockade observed after the injection of Sandimmun, or solvent, is presented as its maximum value, reached at median 17.3, 5.4 and 32.9 min, respectively (table IV), and the degree of blockade still present 45 min after the completion of the injection (125 min since start of infusion). The maximum twitch force regained after terminating the neuromuscular blocking drug infusion is quoted as % of the value seen before paralysis*

	Blockade (%) at constant infusion–response interval		Blockade (%) after injection of Sandimmun or solvent		Maximum recovery (%)
	60 min	75 min	Maximum value	125 min	
Group 1					
Median	48.9	50.7	95.2	93.1	103.6
Quartiles	44.8–50.9	47.7–52.3	93.8–98.7	84.8–97.2	101.2–106.3
Range	43.2–52.2	42.0–52.8	88.6–100	77.1–97.4	99.7–107.8
Group 2					
Median	49.9	51.1	78.0	61.5	104.4
Quartiles	45.9–54.9	47.7–54.3	75.5–84.8	57.2–64.0	100.5–109.7
Range	42.4–58.9	44.2–62.2	72.7–96.8	46.8–81.5	97.7–112.4
Group 3					
Median	48.4	51.3	72.4	69.8	106.2
Quartiles	45.3–52.6	44.2–52.4	64.7–81.5	63.4–80.3	102.9–112.1
Range	42.9–53.7	39.8–53.7	63.9–84.7	61.9–84.7	98.1–114.1

group 1 vecuronium 110 (71–146), group 2 vecuronium 104 (56–122), and group 3 atracurium 250 (207–339).

Potentiation of blockade

The course of neuromuscular blockade after the administration of the interacting agents is given in table III. Blockade was augmented in all cats, the effect being most marked in group 1 (fig. 1).

The maximum potentiating effect of Sandimmun was 2.7 times greater for vecuronium than for atracurium (table IV) and the interaction of Sandimmun with vecuronium was 2.1 times that of the solvent moiety. Forty-five minutes after the end of the injection of the interacting agents, these relative potentiating effects were 2.8 and 6.0, respectively. The differences between group 1 and each of the two other groups were significant. The

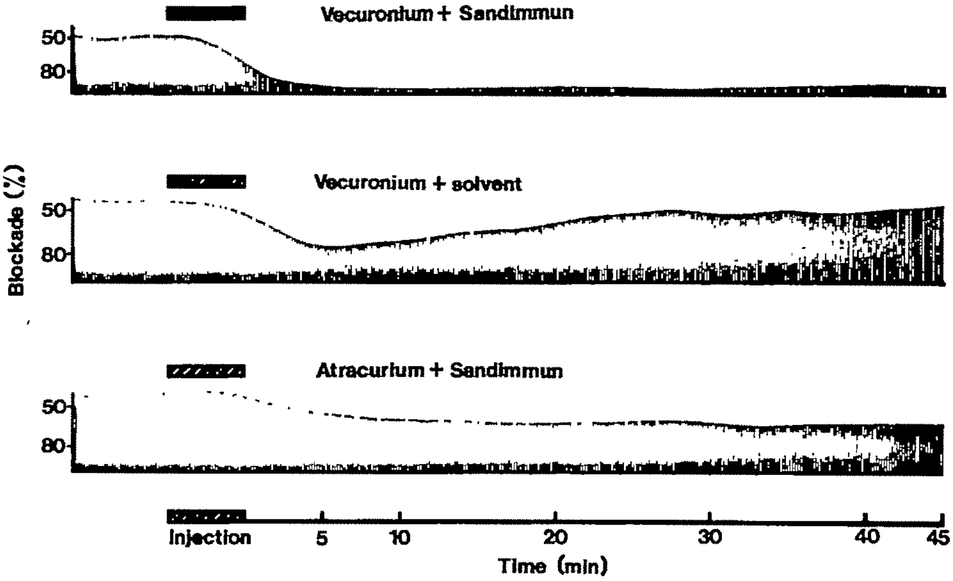

FIG. 1. The effect of Sandimmun (cyclosporin in solvent) 0.8 mg kg^{-1} or the equivalent amount of the solvent moiety, on stable neuromuscular blockade induced by vecuronium or atracurium. Each recording shows the median peak potentiation which was closest to the mean value. Injection = injection of Sandimmun or solvent.

TABLE IV. *Increase in neuromuscular blockade after the injection of Sandimmun, or solvent, calculated as change from preinjection values. The onset of maximum blockade, as well as at the 45-min time interval, is measured from the end of the injection. Results are medians with their 93% confidence limits.* $^{**}P < 0.01$ *and* $^{***}P < 0.001$ *compared with group 1*

Group	Maximum change in blockade (probits)	Onset of maximum blockade (min)	Change in blockade at 45 min (probits)
1	1.685 (1.458–2.347)	17.3 (12.4–24.6)	1.506 (0.886–1.968)
2	0.817** (0.744–0.950)	5.4*** (4.0–6.3)	0.249*** (0.120–0.375)
3	0.614*** (0.538–0.909)	32.9** (25.2–39.6)	0.546** (0.468–0.880)

onset of maximum interaction in group 1 occurred 1.9 times more rapidly than in group 3 and 3.2 times more slowly than in group 2; the differences were significant.

In the atracurium group, an additional equal dose of Sandimmun in three cats produced an increase in twitch depression which ranged from 10.3 to 12.1% of control twitch height, while the first dose had potentiated the blockade by 21.6–24.2%. In four other cats receiving an equivalent amount of solvent, the augmentation of the blockade ranged from 0 to 4.1%, whereas the preceding dose of Sandimmun had produced increases in twitch depression of 20.1–31.0%.

Recovery of neuromuscular function

On cessation of the infusion, neuromuscular blockade exceeded 75% in the cats in group 1 only, and the median 25–75% recovery index in this group was 3.4 min (range 2.2–5.0). The maximum recovery of twitch height was complete and similar in the three groups of animals. The injection of Sandimmun in five cats in group 2 during stable recovery caused no detectable effect on twitch height.

DISCUSSION

The immunosuppressive drug Sandimmun (cyclosporin in solvent) potentiated the neuromuscular blocking actions of vecuronium and atracurium for a prolonged period. The interaction with vecuronium was found to be significantly greater than that with atracurium.

Sandimmun is formulated as cyclosporin in the non-ionic surfactant Cremophor EL and ethanol. We found that the solvent had a rapidly developing potentiating effect on vecuronium-induced blockade, whereas the effect on blockade induced by atracurium appeared to be negligible. Cremophor-containing anaesthetics have previously been reported to decrease the onset time of blockade with the vecuronium analogue, pancuronium, but to have no significant effect on blockade with alcuronium (Gramstad, Lilleaasen and Minsaas, 1981). The proposed mechanism of this action was interference with intravascular binding sites for pancuronium, as a result of the ability of non-ionic surfactants to interact with proteins and biological membranes.

Fragen and colleagues (1983) investigated the effects of Cremophor EL on suxamethonium, vecuronium and pancuronium using an *in vitro* rat phrenic nerve–hemidiaphragm preparation. They found that the dose–response curve for suxamethonium was shifted to the left, whereas the dose–response curves for the non-depolarizing agents were shifted to the right. Inhibition of cholinesterase activity by Cremophor was suggested as a possible mechanism of this action. Assuming no major species differences, our findings indicate that, *in vivo*, Cremophor may have other actions such as effects on drug pharmacokinetics, which more than outweigh its alleged pharmacodynamic antagonism. However, the rapid onset of the interaction makes it unlikely that impairment of the elimination of vecuronium would be a major mechanism. An effect of Cremophor on intravascular binding sites of vecuronium, leaving more drug free for diffusion, remains possible.

The ethanol moiety of the solvent should produce 0.0008% peak concentration in plasma, assuming instantaneous injection to a distribution volume of 0.54 litre kg^{-1} and an open one-compartment kinetic model (Wilkinson et al., 1976). Such concentrations are probably without any significant effect on neuromuscular function. These small amounts of ethanol will also be metabolized in a few minutes.

If we assume that the potentiating effect of cyclosporin plus solvent is merely additive, the effect of cyclosporin *per se* can be deduced by subtracting one effect from the other (fig. 2). This hypothetical time–effect relationship indicates a gradually developing but ultimately substantial, interaction between vecuronium and cyclosporin.

The effect of Sandimmun alone on neuromuscular function was tested after stable recovery in

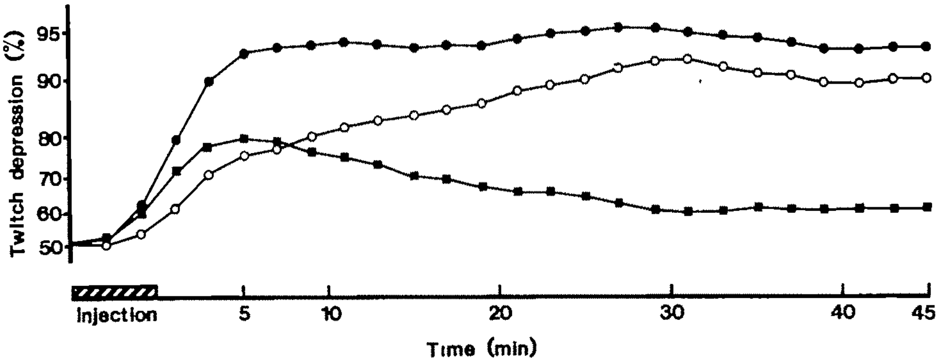

FIG. 2. Deduction of a hypothetical time–interaction curve of vecuronium and cyclosporin (○——○), from the time–interaction relationships of vecuronium–Sandimmun (●——●) and vecuronium–Cremophor (■——■). Results represent the calculated median changes in response at 2-min intervals. Injection = injection of interacting agent.

group 2. No detectable effect was seen. Neither was the depression of the twitch height sustained during recovery from neuromuscular blockade after the discontinuation of the infusion of the neuromuscular blocking agents. This indicates that the interaction between Sandimmun and vecuronium or atracurium, is true potentiation—the augmentation of the action of one drug by a second drug that has no detectable action on its own (Smith, 1981).

The mechanism of the interaction is unclear. Cyclosporin is a neutral, hydrophobic cyclic peptide composed of 11 amino acid residues. It has a strong affinity for cellular and membrane structures, and its protein binding is about 90%. It is eliminated mainly by metabolism in the liver. The metabolism of cyclosporin may be increased or decreased by other drugs (Kahan, 1984). Cyclosporin has been reported to reduce the clearance of prednisolone (Öst, 1984). If, however, cyclosporin was producing an effect on vecuronium only by impairing metabolism, no potentiation would be expected in the atracurium group. Adverse effects by cyclosporin on renal, hepatic and nervous functions have been reported (Kahan, 1984). Thus it follows that there are many potential means by which cyclosporin could interact with vecuronium and atracurium. Elucidation of such mechanisms requires further investigation.

The dose of cyclosporin used in this study was 0.8 mg kg^{-1} administered over 5 min, which is a smaller dose given more rapidly than is usual in clinical practice. Recipients of renal grafts in our hospital receive 2.5 mg kg^{-1} i.v. in the course of 1 h or more, three times on the day of surgery, the first dose being completed before the anastomosis of the renal artery. Since it is acknowledged that, among the common laboratory animals, the cat is the one which most closely resembles man in its response to neuromuscular blocking agents (Bowman, 1964), the interaction of Sandimmun with neuromuscular blockers may be of clinical importance. An appropriate clinical study is indicated.

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EFFECTS OF ENFLURANE AND HALOTHANE ON CARBOHYDRATE METABOLISM IN ISOLATED PERFUSED RABBIT LUNGS

J. L. PATERSON, S. M. SAPSED-BYRNE AND G. M. HALL

It is well recognized that inhalation anaesthetic agents exert metabolic effects on many important organs such as the liver and brain. For example, halothane acts on glycogenolytic (Biebuyck and Lund, 1974), mitochondrial (Cohen, 1973) and microsomal (Hallen and Johansson, 1975) pathways within the liver. Although inhalation anaesthetics are introduced through, and so reach their highest concentrations in, the lungs, there is little information available as to their effects on lung metabolism. The majority of previous work has concentrated on the effects of halothane on the uptake and metabolism of vasoactive amines from the pulmonary circulation (Naito and Gillis, 1973; Bakhle and Block, 1976; Watkins, Wartell and Rannels, 1983). However, more recently it was shown that halothane reversibly inhibits protein synthesis in rat lungs (Wartell et al., 1981; Rannels, Christopherson and Watkins, 1983). The object of the present study was to examine the effects of enflurane and halothane on carbohydrate metabolism in isolated, perfused rabbit lungs.

SUMMARY

Isolated, perfused rabbit lungs were used to investigate the effects of enflurane and halothane on pulmonary carbohydrate metabolism. The development of oedema in the preparation was assessed by continuous measurement of pulmonary artery pressure, airway pressure and lung weight. Ventilation of the lungs with 2% enflurane for 3 h had no effect on the rates of glucose utilization and lactate production and there were only small changes in the indices of oedema. Likewise, ventilation with 1% halothane for 1 h had no effect on the rates of glucose utilization and lactate production, and did not change significantly the concentrations of glycogen, glucose, glycolytic intermediates and high-energy phosphate compounds in lung tissue. Enflurane and halothane, at clinically relevant concentrations, probably do not influence carbohydrate metabolism in the lung.

MATERIALS AND METHODS

Surgical preparation

New Zealand white/lop-eared cross-bred rabbits which had been fed *ad libitum*, were anaesthetized with thiopentone 25 mg kg^{-1} administered through an ear vein. Tracheotomy was performed, a 6-mm diameter flexible, polyethylene cannula was inserted to the trachea and the lungs ventilated with a mixture of 7% carbon dioxide in 93% oxygen. Heparin 1000 u. kg^{-1} was given i.v., the thorax opened, and after the rabbit had been exsanguinated via the right ventricle, the heart and lungs were excised rapidly. A 4-mm diameter flexible, polyethylene cannula was placed in the pulmonary artery from the right ventricle and secured. A similar cannula was passed through the left ventricle and placed in the left atrium. The pulmonary artery cannula was connected to the bubble-trap of the perfusion circuit and that from the left atrium placed in the perfusion reservoir (fig. 1).

The perfusion medium was Krebs–Henseleit high bicarbonate buffer to which was added bovine albumin (Fraction V, Sigma Chemical

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J. L. PATERSON, B.SC.; S. M. SAPSED-BYRNE; G. M. HALL, M.B., B.S., PH.D., C.BIOL., M.I.BIOL., F.F.A.R.C.S.; Department of Anaesthetics, Hammersmith Hospital, Royal Postgraduate Medical School, London W12 0HS.

Correspondence to G. M. H.

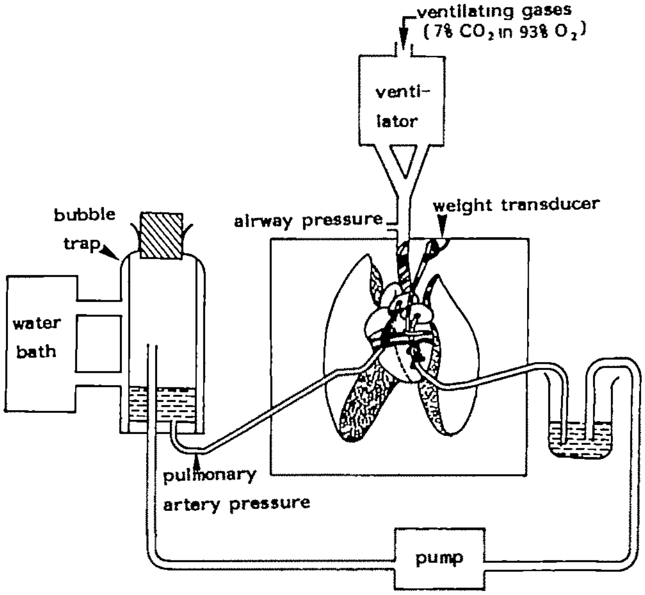

FIG. 1. Perfusion circuit.

Company) and glucose to give final concentrations of approximately 5 g dl^{-1} and 5 mmol $litre^{-1}$, respectively. The perfusate was aerated with the 7% carbon dioxide in 93% oxygen mixture for 1 h before use. The circuit was checked meticulously for air bubbles, which were removed if present. The lungs were suspended from a calibrated weight transducer in a Perspex box so that a continuous measurement of changes in lung weight could be obtained. Pulmonary artery and airway pressures were determined using calibrated pressure transducers.

Perfusion was commenced using a non-pulsatile, recirculating system with the perfusate temperature maintained at 37 °C. The flow rate was 20 ml min^{-1}, which was verified at the beginning and end of each experiment. Ventilation of the lungs was undertaken using the carbon dioxide in oxygen mixture with an end-expiratory pressure of 2 cm H_2O. The ventilator was set initially to deliver a tidal volume of 10 ml kg^{-1} at a frequency of 25 b.p.m. and adjusted to maintain perfusate values in the range pH 7.42–7.51, Po_2 35.9–46.6 kPa and Pco_2 4.9–5.6 kPa. The perfusion pressure in the pulmonary artery was adjusted to 15.0 mm Hg at the start of the study.

The preparation was allowed to equilibrate for at least 1 h before the start of each investigation.

Enflurane study

Eight rabbit lungs were ventilated with the 7% carbon dioxide in 93% oxygen mixture for 3 h and a further eight lungs were studied with the addition of 2% enflurane from a calibrated vaporizer to the gas mixture. Perfusate samples were collected simultaneously every 15 min from the pulmonary artery and left atrium for the determination of glucose, lactate and albumin concentrations in duplicate (Dommes, Watson and Biggs, 1971; Hall et al., 1980). The pulmonary artery pressure, airway pressure and lung weight were noted at each sample time. The exchange of metabolites across the lungs was calculated from the product of the arteriovenous concentration difference of the metabolite and the flow rate and expressed as μmol min^{-1}.

Halothane study

As the results of the enflurane study showed that prolonged ventilation had little effect on metabolite exchange, a shorter period of perfusion was used in this study. Eight lungs were ventilated with the 7% carbon dioxide in 93% oxygen mixture for 1 h and a further eight lungs were studied with the addition of 1% halothane from a calibrated vaporizer to the gas mixture. Samples of perfusate were collected every 15 min to

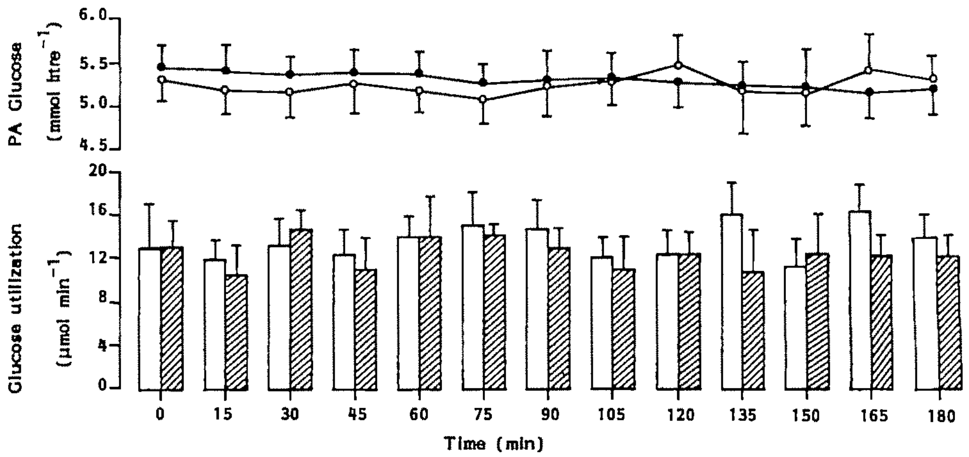

FIG. 2. Mean (±SEM) pulmonary artery glucose concentration (mmol litre^{-1}) and glucose utilization (µmol min^{-1}) during 3 h of perfusion. Control = open circles and open bars; enflurane = closed circles and hatched bars.

determine the exchange of glucose and lactate across the lungs as described above.

At the end of the 1-h perfusion the lungs were frozen rapidly in liquid nitrogen, weighed and freeze-dried to constant weight. The concentrations of glycogen, glucose, glycolytic intermediates and high-energy phosphate compounds in the freeze-dried lung tissue were determined by methods described previously (Hall and Lucke, 1983).

The results are expressed as mean values (±SEM). Statistical analysis of the data was undertaken using two-way or one-way analysis of variance, as appropriate.

RESULTS

Enflurane study

During the 3-h perfusion the increases in pulmonary artery pressure, airway pressure and lung weight were similar in the control lungs and in those ventilated with 2% enflurane (2.7±1.0 and 3.7±1.1 mm Hg; 4.8±1.9 and 2.1±0.6 mm Hg; 0.90±0.25 and 0.64±0.15 g, respectively).

Glucose concentrations in the pulmonary artery were maintained between 5.1 and 5.4 mmol litre^{-1} in the control group and 5.2 and 5.5 mmol litre^{-1} in the enflurane group (fig. 2). Glucose utilization did not change significantly during the period of perfusion (3 h), nor was there a significant difference between the two groups. The mean glucose uptake throughout the perfusion was 13.6±0.5 µmol min^{-1} for the control group and 12.5±0.4 µmol min^{-1} for the enflurane group.

Lactate concentrations in the pulmonary artery varied between 0.70 and 0.90 mmol litre^{-1} in the control group, but were slightly greater in the enflurane group: from 0.87 to 1.14 mmol litre^{-1} (fig. 3). Ventilation with 2% enflurane did not alter significantly the rate of lactate production. Mean rates of lactate efflux for the 3-h perfusion were 8.0±0.3 µmol min^{-1} (control) and 9.7±0.5 µmol min^{-1} (enflurane).

The pulmonary artery albumin concentration varied between 5.24 and 5.46 g dl^{-1}. No arteriovenous difference in albumin concentration was detected in either group.

Halothane study

The pulmonary artery pressure, airway pressure and lung weight did not increase significantly during the short perfusion period of 1 h in either group and there was no significant difference between the groups.

Pulmonary artery glucose concentrations were lower in this study (3.9–4.5 mmol litre^{-1}) and were associated with higher rates of glucose utilization during the perfusion period (19.8±3.0 µmol min^{-1}, control group; 22.5±3.8 µmol min^{-1}, halothane group). Lactate efflux was similar in both groups: 8.2±0.5 µmol min^{-1} (control) and 9.9±1.1 µmol min^{-1} (halothane).

Ventilation of the lungs with 1% halothane for 1 h had no effect on tissue concentrations of

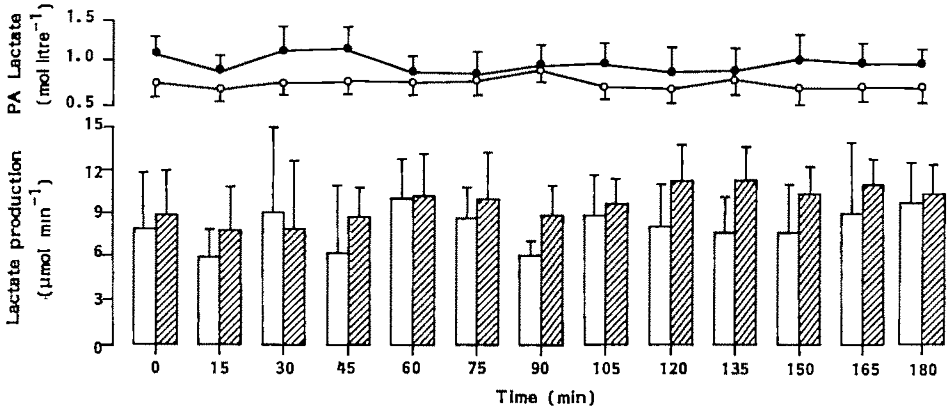

FIG. 3. Mean (±SEM) pulmonary artery lactate concentration (mmol litre^{-1}) and lactate utilization (µmol min^{-1}) during 3 h of perfusion. Control = open circles and open bars; enflurane = closed circles and hatched bars.

glycogen, glucose, glycolytic intermediates and high-energy phosphate compounds (table I).

The pulmonary artery albumin concentration varied between 4.80 and 5.10 g dl^{-1} and no arteriovenous difference was detected in either group. The dry to wet weight ratio of the lungs was 0.16±0.02 in both groups.

DISCUSSION

The results show that ventilating the lungs with 2% enflurane or 1% halothane had no effect on carbohydrate metabolism as assessed by changes in glucose uptake, lactate efflux and tissue metabolite concentrations. The ineffectiveness of halothane in altering carbohydrate metabolism is in contrast to its ability reversibly to inhibit protein synthesis in the lungs (Wartell et al., 1981; Rannels, Christopherson and Watkins, 1983). In the studies of protein synthesis, however, the lungs were ventilated with concentrations of halothane as high as 4% for 3 h (46% inhibition); 1% halothane resulted in only a 10% inhibition in the rate of protein synthesis (Rannels, Christopherson and Watkins, 1983). Obviously, the usefulness of data obtained during ventilation with such high concentrations of halothane must be questionable.

TABLE I. *Mean (±SEM) metabolite concentrations in lungs ventilated with 7% carbon dioxide in 93% oxygen (control) and 7% carbon dioxide in 93% oxygen + 1% halothane (halothane) for 1 h. *Expressed as glucosyl units*

Metabolite (µmol/g dry wt)	Control (n = 8)	Halothane (n = 8)
ATP	2.9±0.9	1.7±0.8
Phosphocreatine	17.4±5.6	21.5±6.7
ΣATP + Phosphocreatine	20.4±6.0	23.2±7.1
ADP	0.66±0.26	0.43±0.34
AMP	0.20±0.10	0.04±0.02
Creatine	0.36±0.17	0.15±0.04
Glycogen*	44.7±8.3	39.7±3.1
Glucose	9.1±1.8	10.8±1.2
Glucose-6-phosphate	0.79±0.43	0.34±0.06
Pyruvate	1.4±0.7	2.0±0.3
Lactate	7.1±1.6	7.1±0.9

The assessment of oedema in the preparation is a vital aspect of any study using perfused lungs (Chang, Wright and Effros, 1981). Most investigators have confined their estimation of oedema to histological examination at the end of the period of perfusion, together with the determination of the dry to wet weight ratio. The ratio is then compared with values obtained from unperfused lungs (Alberti et al., 1978; Woods et al., 1980). This method only gives an estimate of total oedema formation throughout the perfusion, and does not indicate its rate of development. The method of assessment of oedema used in the present study—continuous measurement of pulmonary artery pressure, airway pressure and lung weight—is an improvement on the usual procedure. In particular, the measurement of changes in lung weight was of great value and usually preceded detectable changes in pulmonary vascular resistance. The greatest weight gain recorded during the experiment was 1.5 g, which was only 6% of the lung wet weight.

The ability of the isolated lung to utilize exogenous glucose has been described previously and is influenced by many factors including starvation, the glucose and lactate concentrations of the perfusate, anoxia, ventilation and insulin (Alberti et al., 1978). It has been assumed that the importance of circulating glucose is related to the small amounts of stored glycogen and triglyceride (Datta, Stubbs and Alberti, 1980). The glycogen contents of the lungs found in the halothane study (table I) confirm the small amount of stored glucose. If the rates of glucose utilization found in the halothane study were supported solely from glycogen, then they would provide sufficient glucose for only 10 min. Lactate is quantitatively the major product of glucose metabolism by lung tissue and can account for up to 50% of the glucose utilization (Fisher and Dodia, 1984). The metabolite concentrations obtained in the halothane study (table I) provide supporting evidence for the glycolytic fate of glucose taken up from the perfusate. After corrections are made for conversion from dry to wet weight, the appropriate concentration gradients were present between lung and perfusate for both metabolites. Fisher and Dodia (1984) noted the extreme sensitivity of lactate production by isolated lungs to the circulating lactate concentration with a decrease from 58% to 5% as the lactate concentration of the perfusate increased from 0 to 2 mmol litre^{-1}. At high circulating lactate values (> 5 mmol litre^{-1}) the lungs show an uptake of lactate and so probably have an important role in the clearance of this metabolite during physiological and pathological lactic acidosis (Datta and Alberti, 1979).

It is important to note that the rates of substrate utilization found in the present study occurred in the presence of high oxygen tensions in the perfusate. However, previous work has shown little effect of changes in oxygen tension on lung metabolism, providing that neither hypoxia nor hyperbaric oxygen are used (Bassett and Fisher, 1979; Watkins and Rannels, 1979).

In conclusion, the data suggest that enflurane and halothane at clinically relevant concentrations, have no effect on carbohydrate metabolism in isolated, perfused rabbit lungs. Direct determination of the glycolytic rate in the lung using radioactivity labelled glucose should be undertaken to confirm these observations.

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A MICROPROCESSOR-CONTROLLED ANAESTHETIC VAPORIZER

C. E. W. HAHN, E. PALAYIWA, B. R. SUGG AND D. LINDSAY-SCOTT

SUMMARY

A microprocessor-controlled anaesthetic vaporizer is described. Fresh gas is mixed in the correct proportions using two pulsed solenoid valves and a proportion of this passes through a third pulsed solenoid valve and is bubbled through liquid halothane. The temperature of the liquid agent is measured and the pulse frequency is modified to give the correct vapour concentration for the set flow rate and measured temperature. Initially, the vapour was produced by bubbling fresh gas through the agent in a conventional halothane bottle. However, because of the large liquid volume available, nitrous oxide was found to dissolve in large quantities in the halothane. A small volume vaporizer which was continually replenished from a reservoir was designed. Measurements of the vapour concentrations emerging from such a vaporizer were made and were found to agree with the set values ±0.1% v/v.

Conventional anaesthetic vaporizers channel the fresh gas flow along two pathways, one through the vaporizing chamber and one through a bypass. These are then recombined in a common outlet. The conventional vaporizer chamber usually contains wicks so that gas passing through the chamber passes over their surfaces, as well as that of the liquid agent itself, and so becomes saturated with anaesthetic vapour. The total vapour concentration will depend on the gas flow in each of the pathways, as well as the saturated vapour pressure of the agent in the vaporizing chamber. As vaporization proceeds, the temperature of the agent, and hence its saturated vapour pressure, will decrease and manufacturers have incorporated temperature compensators into their vaporizer design such that the fresh gas flow through the two pathways is varied as the temperature decreases. This causes more fresh gas to be delivered through the vaporizing chamber, and so maintain a constant vapour concentration at the vaporizer outlet.

In practice, these pathways are complex in a conventional vaporizer, and vaporizers can only be relied on to produce accurate vapour concentrations over a limited range of working conditions. Some vaporizers show a marked increase in output concentration when the flow rate decreases, and the output concentration of some vaporizers shows a marked dependence on the carrier gas used as the fresh gas supply (Stoelting, 1971; Diaz, 1976; Lin, 1979; Stoelting and Nawaf, 1979; Knill et al., 1980; Prins et al., 1980; Palayiwa, Sanderson and Hahn, 1983). However, in vaporizers in which the fresh gas flow rates through the bypass and vaporizing chamber are controlled separately, and where the temperature of the vaporizing chamber is measured, the output concentration of the vaporizer can be predicted accurately. This requires the anaesthetist to perform fairly complex calculations, and to adjust manually for temperature changes as the temperature of the vaporizing chamber decreases.

In recent years (Cooper et al., 1978; Anthony, 1982) a new anaesthetic delivery system has been described which has been termed the Boston Anesthesia system. In this system, mixtures of oxygen and nitrous oxide are produced by "digital valves" (Lundsgaard, Einer Jensen and Juhl, 1977; Cooper et al., 1978) and liquid anaesthetic is injected to this gas stream in metered volumes. The injection device is an automatic fuel injector,

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C. E. W. HAHN, M.A., B.SC., M.SC., D.PHIL.; E. PALAYIWA, M.A.; Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headington, Oxford OX3 9DU. B. R. SUGG, B.SC.ENG.; D. LINDSAY-SCOTT; Penlon Limited, Radley Road, Abingdon, Oxon.

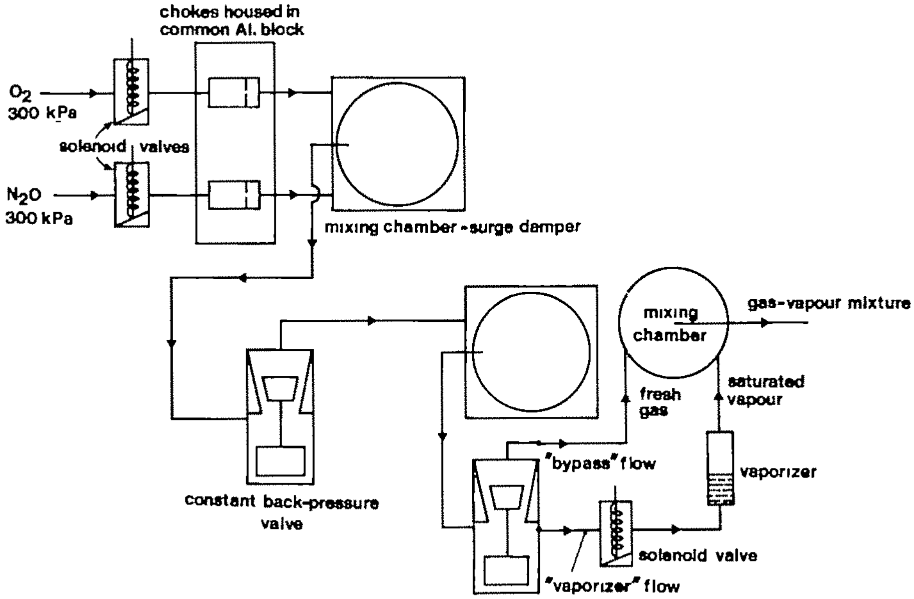

FIG. 1. Schematic diagram of the gas mixing, flow stabilizing and vaporizer apparatus.

modified for use with volatile anaesthetics. The injector is controlled by a microprocessor, the liquid anaesthetic being atomized into a chamber as it emerges from the injector, and complete vaporization achieved in a copper vaporizing coil. Temperature compensation is not necessary (Cooper et al., 1978.) With this design, the liquid anaesthetic had to be supplied in a special prefilled plastic container, which was translucent to permit observation of the liquid level. It was envisaged that the cannisters would be filled or refilled only by a manufacturer or distributor, to avoid the hazard of misuse.

We describe, in this paper, an alternative system delivering a predicted concentration of a volatile anaesthetic agent by means of a simple vaporizer, which is controlled by a microprocessor. Although this system used halothane as the volatile agent, it could equally well be used for other agents, such as enflurane or isoflurane.

MATERIALS AND METHODS

Apparatus

Fresh gas supply

Oxygen and nitrous oxide were supplied to the vaporizer by an electromagnetic solenoid valve gas-mixing apparatus, controlled by a microprocessor, as described in a previous paper (Palayiwa et al., 1986). The solenoid valves were pulsed open for a set time, so that they passed a constant volume of gas for each "open" period. By varying the pulse frequency, the flow rate for each gas was controlled, thus producing accurate nitrous oxide–oxygen gas mixtures with known concentrations over a wide range of constant flow rates. The gases passed through a double mixing chamber–damping system so that any pulsatility was smoothed. The gas emerging from the gas mixer–pulse damper system passed through a special constant pressure device, described in our previous paper, which maintained a constant pressure of 9.81 kPa (100 cm H_2O) upstream of the vaporizer. A schematic diagram of the gas supply system is presented in figure 1, and highlights the major components.

The gas supply for the actual vaporizer was taken off beneath the second constant pressure valve. The float of the valve was placed in a continuously tapering tube so that, if the upstream pressure were to decrease, gas would still bypass the vaporizer and, therefore, prevent the delivery of saturated vapour. The vaporizer gas supply passed through a solenoid valve, which was pulsed at a frequency controlled by the microprocessor, and this gas then bubbled through the liquid agent in the vaporizer. The gas/vapour emerging from the vaporizer then entered a steel mixing chamber. The fresh gas, which bypassed the vaporizer, entered on the opposite side of the mixing chamber, both entry ports being arranged tangentially opposite each other, so that gases and vapour travelled in toroidal paths, to ensure good mixing. The mixing chamber was similar in operation to those used in the gas mixing system, except that the upper wall of the chamber was fixed and contained the gas outlet.

Early vaporizer design

Initially, a simple halothane bottle (as supplied by the manufacturer) was used as the vaporizer, and the fresh gas was simply bubbled through the liquid agent. A special screw cap held the tubes for entry and exit of the gases, and a thermistor was immersed in the liquid in a thin stainless steel tube. Temperature was fed into the microprocessor as a "feedback" control.

The microprocessor contained a program which was written so that the required oxygen concentration, total gas flow rate, and halothane concentration could be entered via a keyboard. The program then calculated the pulsing regimen for the oxygen and nitrous oxide gas mixing valves and used the vapour pressure–temperature relationship of the halothane (Hill, 1976), together with the knowledge of the total gas flow rate into the liquid agent, to calculate the pulsing rate necessary to give a required vapour concentration. These calculations are contained in the Appendix, and assume that the vapour emerging from the vaporizing chamber is fully saturated. The temperature was read every 2 s and the vaporizer valve frequency was adjusted to accommodate any change in temperature as the vaporization process took place.

This simple vaporizer design was finally discarded, for reasons given in the discussion section, and a final vaporizer design was developed.

Final vaporizer design

The final vaporizer design is shown in figure 2. In concept, this design is very similar to that of a conventional carburretor. It is machined out of a cylindrical copper rod. The liquid anaesthetic enters a float chamber, where the float activates a needle valve, which controls the input of liquid anaesthetic agent to the vaporizer. The total volume of liquid anaesthetic in the vaporizer is set to approximate 10 ml, and the needle input valve is connected to either a halothane bottle, or a metal halothane reservoir tank, via a flexible tube. The float chamber connects directly with a small vaporizing chamber, which also contains a sintered gas inlet port, positioned so that the fresh gas bubbles through the liquid anaesthetic contained in the vaporizing chamber.

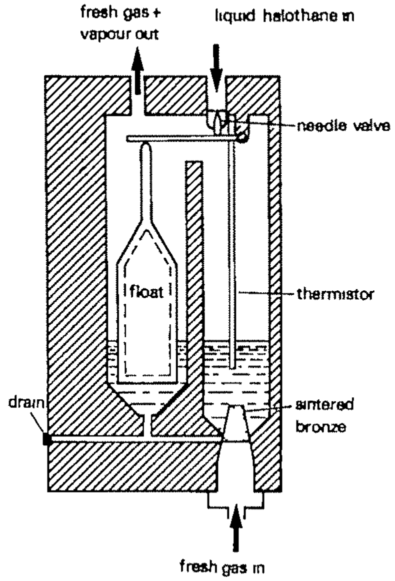

FIG. 2. Schematic diagram showing the final vaporizer design in vertical cross section.

In the event of the chamber overfilling, a second safety valve comes into action and liquid halothane flows out through a spill tube. Spillage can be returned by gravity to the metal reservoir tank, although this is not possible if the halothane bottle is used as the reservoir. A thermistor is mounted in the copper block to monitor the temperature of the vaporizer, and this information is fed directly to the microprocessor. Anaesthetic vapour leaves the vaporizer block assembly through a port in its upper surface, and is fed into the mixing chamber illustrated in figure 1.

Experimental Procedure

Measurements of vapour concentration were undertaken with a respiratory mass spectrometer (Centronic MGA 200), with halothane being measured on mass number 117. The mass spectrometer was calibrated against a small portable refractometer (Riken Gas Indicator), as described by Palayiwa, Sanderson and Hahn (1983).

The volume of a pulse of gas from the solenoid valve was measured first of all in the absence of the vaporizer, by pulsing gas into a wet spirometer (P. K. Morgan Ltd) and measuring the total volume. The open time of the solenoid valve was set at 100 ms. The actual pulse volume delivered by the solenoid valve when connected to the vaporizer was deduced empirically by inserting the pulse volume, in the absence of the vaporizer, to the computer program and then comparing the vapour concentration delivered by the vaporizer with the value "set" by the microcomputer. The difference between the "actual" and "set" vapour concentrations was used to determine the pulse volume delivered by the solenoid valve.

For both the early and final designs of vaporizer, different total fresh gas flow rates and different oxygen–nitrous oxide mixtures were passed through the vaporizer, and the final halothane concentration was measured at the exit to the mixing chamber. Flow rates were varied between 2 and 16 litre min^{-1}, and the oxygen concentration was varied between 20% and 100%, the balance being nitrous oxide.

RESULTS AND DISCUSSION

Solenoid Valve Pulse Regimen

It was found that, for total gas flows in excess of 2 litre min^{-1} (flow conditions where the constant pressure valve works well, and maintains 100 cm H_2O forward pressure), the pulse volume delivered by the solenoid valve was constant and equal to 7.2 ml. For flow rates less than 2 litre min^{-1}, the open time for the valve was reduced to 50 ms in order to decrease fluctuations in the vapour concentration at the output of the vaporizer. Under these conditions, the pulse volume was found empirically to be given by the equation $Vp = 2.75 + 1.01\ O_2/100$ where Vp is the pulse volume (ml), and O_2 is the oxygen concentration in % v/v. This formula was used in the microprocessor software to calculate the predicted halothane composition delivered by the vaporizer, for flow rates less than 2 litre min^{-1}.

Early vaporizer design

The initial results with the early vaporizer design looked promising, except that, at flow rates less than 5 litre min^{-1}, the vapour concentration delivered by the vaporizer appeared to be totally unpredictable. Further investigations made it clear that a change in carrier gas concentration produced a transient change in the output of the vaporizer. In some cases, this was very large, such that the vaporizer output concentration decreased to half of its original value when the carrier gas was suddenly changed from 100% oxygen to 21% oxygen in nitrous oxide. At low flow rates, this transient change was prolonged, lasting up to 30 min. Further investigations revealed that this phenomenon was the result of the high solubility of nitrous oxide in halothane (Gould, Lampert and Mackrell, 1982; Lampert et al., 1982; Palayiwa, Hahn and Sugg, 1985). When nitrous oxide was bubbled into the halothane in the halothane bottle, the emerging halothane concentration decreased because large quantities of nitrous oxide were simply dissolving in the liquid. The halothane concentrations returned to their set values only when nitrous oxide saturation in halothane was reached.

This effect was seen much more markedly in this type of vaporizer than in conventional vaporizers, because of the size of the bottle and because the gas was physically bubbled through halothane. In conventional vaporizers, the gas is passed over the surfaces of the wicks and this physically limits the quantity of liquid halothane available to absorb nitrous oxide.

One possible solution was to bubble oxygen alone through the vaporizing chamber and, thus, avoid the nitrous oxide absorption effect. However, this would have entailed a redesign of the system, and it would have meant that, under certain circumstances, the bypass would contain a hypoxic mixture. This would be dangerous if there were any failure of the vaporizer valve, such that this hypoxic mixture was the only gas delivered to the patient. Also, since our method of gas analysis (to be published in a following article) required that the oxygen–nitrous oxide mixture passed through the vaporizer, it meant that the vaporizer had to be redesigned, with a small volume of halothane only available for nitrous oxide absorption.

Final vaporizer design

The final design has already been described, and is illustrated in figure 2. The volume of the vaporizing chamber was drastically reduced, to 10 ml, so that the transient effect would be small and shortlived. This reduction in halothane volume was found to decrease the duration of the transient effect to 1 or 2 min at the lowest flow rate used (1 litre min^{-1}) and to a few seconds at flow rates greater than 10 litre min^{-1}.

Also, using a large block of copper for the construction of the vaporizer increased its heat capacity considerably and, therefore, reduced the rapidity of cooling—which occurred in the early design. However, cooling of the liquid agent was still a problem since, if the vaporizer is to be used for enflurane, it should be able to deliver 7% enflurane at a total fresh gas flow of 16 litre min^{-1}. This requirement introduces its own problems, since it is not advisable to reduce the period of the vapour valve to less than twice its open-time, because opening and closing transients for the valve become important. In effect, this restriction means that the maximum gas flow available for flow through the vaporizer is a little over 2 litre min^{-1}, since the volume of a 100-ms pulse is 7.2 ml.

Assuming a maximum flow of 2 litre min^{-1} through the vaporizer, and 14 litre min^{-1} through the bypass, and a saturated vapour pressure of 25% of an atmosphere, then 2.5 litre of gas emerged from the vaporizer and this contained 25% vapour. The total vapour concentration is therefore given by $2.5 \times 25/16.5$, which is approximately 4% v.v. This would be the maximum concentration available, and would be sufficient when halothane is the agent used. However, in an enflurane vaporizer this concentration could only be increased by introducing a heating device to the vaporizer construction. The simplest way to achieve this would be by mounting a thermostatically-controlled heater in the copper block, and maintaining the temperature of the vaporizer at a preset level. Further investigations are necessary to determine whether this method would work well.

Vaporizer Performance

Figure 3 shows an illustration of the variation in halothane concentration with time, for different total fresh gas flow rates. Some pulsatility is evident, because of the nature of the pulsed gas flow through the vaporizer. However, the pulsing is rapid and the fluctuations will be averaged out in the inspiratory period. The average delivered concentration was equal to the value predicted by the microprocessor algorithm software. At high flow rates, the frequency of the pulsing of the vapour valve was high, and the fluctuations illustrated in figure 3 could only be detected by instruments with a fast response time such as a mass spectrometer, or an "Emma" Vapour Analyser.

Table I illustrates the performance of the vaporizer for a 50% nitrous oxide in oxygen gas mixture at flow rates of 2, 5, 10 and 16 litre min^{-1}. It is clear that the vaporizer was performing very well at all flow rates, and that the predicted and measured values were in agreement to within 0.1% v/v.

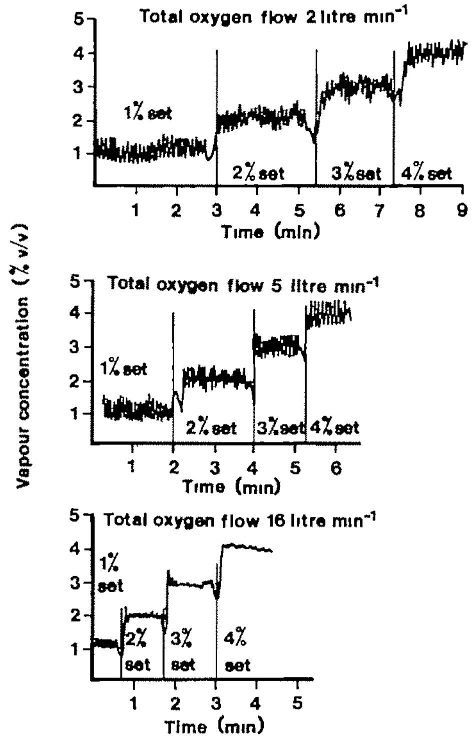

FIG. 3. Plot of the variation in halothane concentration with time for different oxygen flow rates and set concentration values, when the oxygen concentration was 20% v/v.

Figure 4 illustrates the performance when the total fresh gas flow rate is set at 10 litre min^{-1} and the oxygen in nitrous oxide concentrations are varied between 20, 50 and 100%. Again, the measured against predicted halothane concentrations did not vary by more than 0.2% v/v.

Whilst we have retained the conventional volumetric percentage expression of vapour concentration, this type of vaporizer provides a

TABLE I. *Performance of the vaporizer. Measured vapour concentrations at four flow rates of a 50% nitrous oxide in oxygen gas mixture*

Set vapour concentration	Flow rate (litre min^{-1})			
	2	5	10	16
1.0	1.0	1.1	1.0	1.1
2.0	2.0	2.1	2.1	2.0
3.0	3.1	3.1	3.0	3.1
4.0	4.1	4.1	4.0	3.9

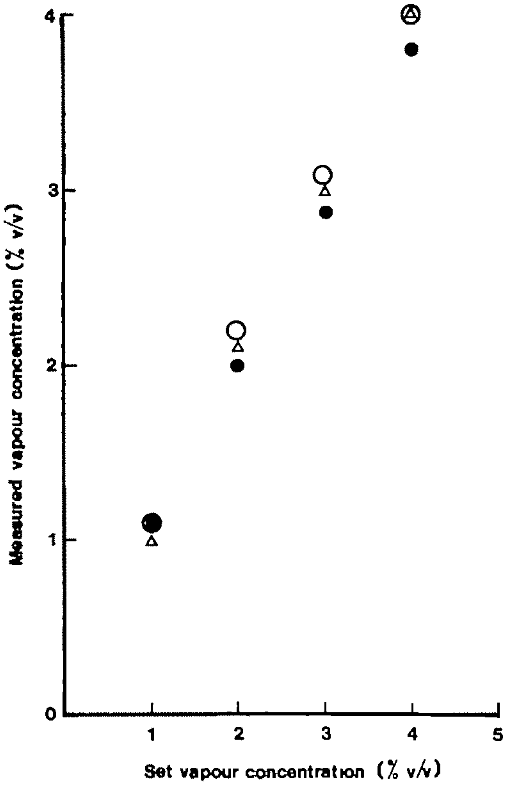

FIG. 4. Plot of measured halothane concentration against set value, at a flow rate of 10 litre min^{-1} and oxygen concentrations of 20% (●), 50% (△) and 100% (○).

controlled flow of saturated vapour at a known temperature and could, therefore, readily be adapted to calibration in mass flow terms; for example, for use with totally closed breathing systems.

CONCLUSIONS

The general conclusion is that it is possible to design a new type of vaporizer constructed on the copper kettle principle, which is controlled by a microprocessor, and yet can deliver predictable and accurate vapour concentrations in the clinical range. The principle of using the vapour pressure–temperature relationship for a particular anaesthetic agent as the feedback control for the vaporizer has been shown to be practical at both high and low fresh gas flow rates. This design should provide an alternative method for manufacturers to produce anaesthetic vaporizers, without resorting to complicated engineering specifications, and complicated automatic temperature correction devices.

APPENDIX

CALCULATION OF VAPOUR VALVE PULSE RATE

Let the total fresh gas flow be F, and the required vapour concentration (% v/v) be C. The volume flow rate of vapour added to the fresh gas flow, V, is given by:

$$C = (V \times 100)/(F + V)$$

Hence,

$$V = F \times C/(100 - C)$$

If the saturated vapour pressure of the agent (% v/v) is given by S, then for a flow rate, X, into the vaporizer, the volume of agent added will be given by:

$$V/(X + V) = S/100$$

Hence

$$X = V(100 - S)/S$$

Therefore, by substitution:

$$X = F \times C(100 - S)/(S(100 - C))$$

Since the pulse size is 7.2 ml, the frequency with which the vapour valve must pulse is $X \times 1000/7.2 \times 60$ Hz.

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GASEOUS HOMEOSTASIS AND THE CIRCLE SYSTEM

Factors Influencing Anaesthetic Gas Exchange

C. M. CONWAY

SUMMARY

A mathematical model of a subject breathing from a circle system has been used to follow the course of anaesthetic uptake during the simulated administration of 60% nitrous oxide, 2% halothane and 2% methoxyflurane, under non-rebreathing conditions and with fresh gas flows to the circle system of between 8 and 0.25 litre min^{-1}. Compared with the non-rebreathing state, the use of a circle system reduced the initial rate of increase of alveolar towards fresh gas anaesthetic concentration, and the rate of increase in body anaesthetic content. The degree of reduction became more marked as fresh gas flow was reduced, and as agents of increasing blood solubility were used. These effects of a circle system were influenced by the volume of the circle system and the composition of gas initially present within the system. When the circle system was in use there were increases in the magnitude of both the concentration effect and the second gas effect which were related to the magnitude of fresh gas flow. The use of a circle system augmented the effects of changes in cardiac output and reduced the effects of changes in ventilation on the alveolar concentrations of the anaesthetic. These influences of a circle system were also dependent on the magnitude of fresh gas flow. The degree of augmentation of the effects of cardiac output decreased with increasing blood solubility of the agent in use, whilst the limitation of the effects of ventilation was greatest with the agent of highest blood solubility. Both under non-rebreathing conditions and with the circle system in use, the effects of cardiac output and ventilation were greater with 2% nitrous oxide than with 60% nitrous oxide, and were also greater when gases were given separately than when administered in combination.

When an inhaled anaesthetic agent is administered at a constant inspired concentration, its uptake in the body is conveniently studied by examining the rate of increase in the alveolar concentration of the anaesthetic towards the inspired concentration, and the changes in the body content of that agent. The various factors governing uptake under these conditions were formally described by Kety (1950, 1951). Important variables which influence the rate of increase in the alveolar concentration of an inhaled anaesthetic are the inspired concentration, alveolar ventilation, cardiac output and the solubility of the agent in body tissues, especially blood. Of lesser importance are the concentration effect, which relates the rate of increase of alveolar towards inspired concentration to the magnitude of the inspired concentration (Eger, 1963), and the second gas effect, which is concerned with the influence that the uptake of one gas in the alveolar space has on the uptake of other simultaneously administered gases (Epstein et al., 1964; Stoelting and Eger, 1969).

The factors influencing anaesthetic uptake have most commonly been evaluated using a constant inspired anaesthetic concentration. Some studies have considered uptake when alveolar anaesthetic concentration is maintained constant (Eger and Guardagni, 1963; Lowe, 1972, 1979). The factors governing uptake under these conditions do not differ from those described above. With a constant alveolar anaesthetic concentration, the amount of an agent taken up by the body per breath will be equal to the product of the inspired-to-alveolar anaesthetic concentration difference and the alveolar ventilatory volume per breath. If constancy of alveolar gas concentration is maintained by adjustment of the inspired concentration, then

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C. M. CONWAY, M.B., B.S., F.F.A.R.C.S., D.A., Department of Anaesthetics, Charing Cross & Westminster Medical School, Westminster Hospital, London SW1P 2AP.

uptake is apparently independent of alveolar ventilation.

When anaesthetic agents are administered using a circle system, the inspired anaesthetic concentration is likely to vary throughout the administration. The factors influencing anaesthetic uptake under these circumstances were explored by Eger (1974). He showed that the rate of increase in the alveolar concentration of administered agents was influenced by the magnitude of the fresh gas flow to the circle system, and that the use of a circle system modified the effects of changes in ventilation and cardiac output on uptake.

The present study is an extension of that of Eger. It examines the uptake of three agents—nitrous oxide, halothane and methoxyflurane—in a model of a subject attached to a circle system and in relation to fresh gas flow and composition, the composition of gas in the system at the start of administration, the volume of the circle system, cardiac output and ventilation.

MATERIALS AND METHODS

The model used in these studies has been described previously (Conway, 1986a, b). The subject portion is based upon model P of the circulation–time models of anaesthetic uptake described by Mapleson (1973). This is a multicompartmental model in which gas concentration and content in each tissue compartment are calculated at each heart beat, utilizing Henry's law, the law of conservation of matter, an assumed tension equilibrium for each agent in the components of each compartment and the known solubilities of the agent in the various body tissues. It is assumed that all carbon dioxide entering the circle system is fully absorbed, and all fresh and expired gas in the system is uniformly mixed. Volatile agents are assumed to be administered by fully efficient vaporizers placed in the fresh gas flow line.

Except where otherwise stated, the fresh gas concentration of nitrous oxide was 60% and that of both halothane and methoxyflurane was 2%. The reference values of the relevant body and circle system variables are given in table I. Anaesthetic uptake has been evaluated by examining the changes in alveolar anaesthetic concentration and body anaesthetic content during simulated administrations of 30 min duration. The studies described here have been carried out both with the circle system initially free of anaesthetic agent and with the system initially filled with gas of the same composition as fresh gas. At the start of each study the subject model was assumed to be free of nitrogen. Body content of anaesthetic agent has been expressed at BTPD as the total amount present at the end of each breath, and equals the sum of the amount present in the functional residual capacity and the amounts dissolved in blood and body tissues.

TABLE I. *Subject and circle system variables used in the model*

Subject variables	
Body weight	70 kg
Cardiac output	5 litre min^{-1}
Minute volume	6 litre min^{-1} BTPS
V_D/V_T ratio	0.4
FRC	2 litre BTPS
V_{O_2}	0.2 litre min^{-1} STPD
V_{CO_2}	0.16 litre min^{-1} STPD
Respiratory rate	16 b.p.m.
Heart rate	64 beat min^{-1}
Circle system variables	
Initial volume	6 litre ATPD
Minimum volume	5 litre ATPD
Maximum volume	7 litre ATPD

The influence of fresh gas flow was determined by comparing uptake at fresh gas inflows to the circle system of 8, 4, 2, 1 and 0.5 litre min^{-1} with uptake under non-rebreathing conditions. With halothane and methoxyflurane a fresh gas flow of 0.25 litre min^{-1} was also used. These studies were performed with an initial circle volume of 6 litre and with the system both initially free of the agent being used and primed with gas of the same composition as fresh gas. The influence of the volume of the circle system was evaluated by repeating these studies with circle systems of initial volumes of 3 and 12 litre.

The concentration effect was examined with fresh gas concentrations of 60 and 6% nitrous oxide, under non-rebreathing conditions and with fresh gas flows to the circle system of 0.5 to 8 litre min^{-1}. Second gas effects were examined by comparing the uptake of nitrous oxide and halothane when given separately and in combination. The effects of variations in cardiac output and ventilation were studied using values of cardiac output and minute ventilation of one-half, and double, the values of these variables shown in table I. These studies were performed under non-rebreathing conditions and with fresh gas flows of 1, 0.5 and (with the volatile agents) 0.25 litre min^{-1}. The nitrous oxide portion of this study was repeated with a fresh gas nitrous oxide concentration of 2%. The effects of changes in cardiac output and ventilation on halothane homeostasis were compared when this gas was given in oxygen, and in combination with 60% nitrous oxide.

RESULTS

The ratios of alveolar to fresh gas anaesthetic concentrations for the three agents under non-rebreathing conditions and with the circle system initially free of the agent in use and supplied with a range of fresh gas flows are shown in figure 1. The corresponding changes in body anaesthetic content are shown in figure 2, whilst the inspired anaesthetic concentrations during these studies when the circle system was in use are shown in figure 3. Figures 4 and 5 show the alveolar and inspired anaesthetic concentrations when these studies were performed with the circle system initially filled with fresh gas. Figure 6 shows the patterns of change in the gas concentrations of the three agents in the circle system when administered through systems of volumes of 3 and 12 litre, supplied with a fresh gas flow of 1 litre min^{-1}, and with the circle system initially both primed and unprimed with fresh gas. Figure 7 shows the related alveolar gas concentrations.

The effects of 10-fold changes in the nitrous oxide concentration of the fresh gas on the rate of increase of alveolar towards fresh gas concentration under non-rebreathing conditions and with fresh gas flows of 4 and 2 litre min^{-1} are shown in figure 8. Figure 9 shows the rates of change of alveolar anaesthetic concentration when nitrous oxide and halothane were administered separately, and in combination, under non-rebreathing conditions and with a circle system supplied with fresh gas flows of 4 and 2 litre min^{-1}.

The effects of an increase and decrease in cardiac output on alveolar anaesthetic concentrations, both under non-rebreathing conditions and with the circle system supplied with a fresh gas flow of 1 litre min^{-1}, are shown in figure 10. The corresponding results of changes in ventilation are shown in figure 11. In figure 12 the effects of changes in cardiac output and ventilation under these conditions and at fresh gas flows of 0.5 and 0.25 litre min^{-1} have been plotted as a histogram, to show for each agent the effects of changes in ventilation and cardiac output on alveolar anaesthetic concentrations as the percentage change from the control alveolar concentration at the end of 30-min administrations. Figure 13 compares, as a similar histogram, the effects of cardiac output and ventilation on alveolar nitrous oxide concentration when this gas was administered at fresh gas concentrations of 60% and 2%, whilst figure 14 shows the effects of changes in cardiac output and ventilation on alveolar halothane concentrations when 2% halothane was administered in oxygen and with nitrous oxide.

DISCUSSION

The fresh gas flows and compositions used in the studies described in this paper are unlikely to be followed in clinical practice. It is rare for the clinician to administer a fixed concentration of an inhalation agent, or to use a fixed low fresh gas flow throughout an administration. The rigidly controlled conditions that have been used here are necessary to elucidate the various influences of the use of the circle system on gas uptake.

The three agents used in these studies have been chosen as exemplifying agents of low, intermediate and high solubility in blood. Under non-rebreathing conditions the blood : gas partition coefficient of an inhaled anaesthetic agent markedly influences the course of uptake. The findings of this study demonstrate that the magnitude of the various influences of a circle system upon the uptake process are similarly affected by blood solubility.

Figure 1 shows that, compared with the non-rebreathing state, the rate of increase of alveolar anaesthetic tension is decreased during the use of a circle system. The magnitude of this reduction is a function of the solubility in blood of the agent being used, being least with nitrous oxide and greatest in the case of methoxyflurane. With halothane and methoxyflurane the rate of increase of alveolar anaesthetic concentration decreased as the fresh gas flow to the circle system was reduced. This was also true in the case of nitrous oxide early in its administration. With fresh gas flows greater than 1 litre min^{-1}, alveolar nitrous oxide concentration eventually increased to exceed fresh gas concentration. The modifications in the rates of increase of alveolar concentration for each agent are mirrored in the changes in body anaesthetic content (fig. 2) and are related to the change in circle system (and thus inspired) gas concentrations (fig. 3).

Figures 1–3 show the time-course of events with the circle system initially free of anaesthetic

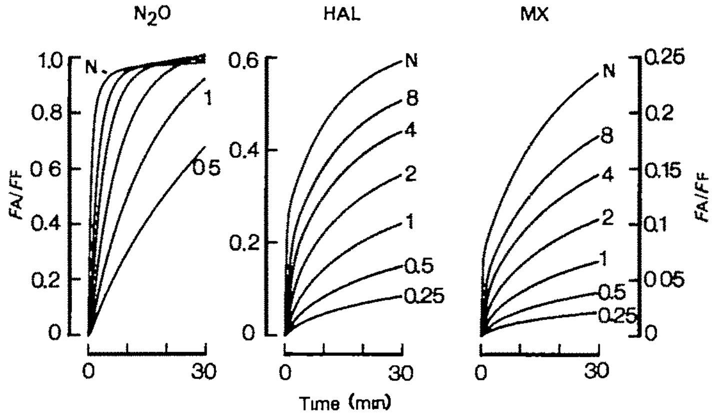

FIG. 1. Alveolar to fresh gas concentration ratios during 30-min administrations of 60% nitrous oxide, 2% halothane and 2% methoxyflurane. At the start of each administration the circle system was free of the agent being used. Note the different y-axis scaling factors. In this and succeeding figures the curves marked N refer to non-rebreathing conditions, whilst the figures against the other curves refer to fresh gas flows in litre min^{-1}.

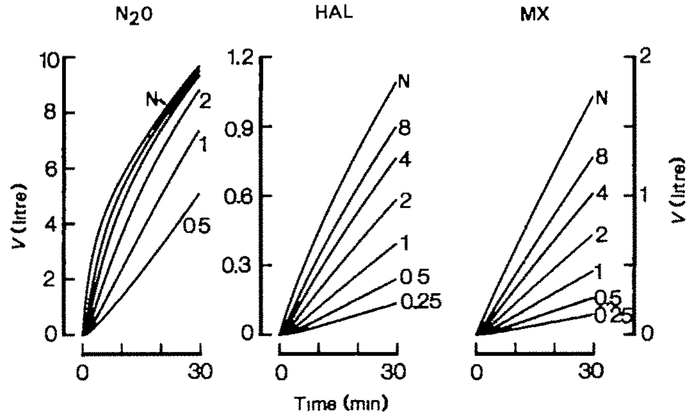

FIG. 2. Total body anaesthetic content (V) (litre BTPD) associated with the administrations shown in figure 1.

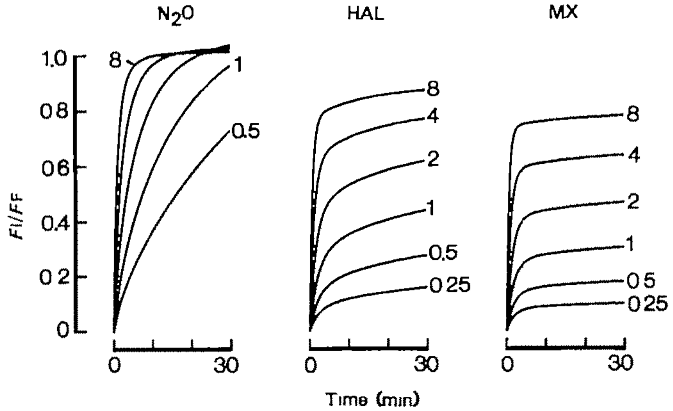

FIG. 3. Inspired to fresh gas concentration ratios during the circle system administrations shown in figure 1.

agent. A somewhat different course of events occurs when, at the start of administration, the circle system contains some of the agent in use. Figures 4 and 5 show the changes in alveolar and inspired anaesthetic concentrations when the circle system is initially filled with gas of the same composition as fresh gas. Gas within the circle system acts as a reservoir which can, in part, satisfy the early uptake requirements of the subject. At the start of administration gas concentrations in the circle system decrease from their initial values, as uptake by the subject at this time exceeds the amount of agent entering the system in the fresh gas. The degree of this decrease increases as fresh gas flow is reduced, and also increases with increasing bood solubility of the agent. Later in the administration, as uptake requirements by the subject decrease, anaesthetic concentrations in the circle system increase towards the concentration in the fresh gas, and the rate of input of anaesthetic agent to the circle system equals and then exceeds its rate of removal. With nitrous oxide and with fresh gas flows of 1 litre min^{-1} or more the gas concentration in the circle system at the end of a 30-min administration exceeds the concentration in the fresh gas.

The interactions between the inspired concentration of an anaesthetic, its alveolar concentration and its uptake by body tissues shown in these five figures demonstrate the overriding influence of the circle system on anaesthetic uptake. Uptake of an agent by a subject during the use of a circle system will, of necessity, reduce the amount of that agent remaining within the circle system, and tend to reduce the concentration of that agent within the circle system. The consequent diminu-

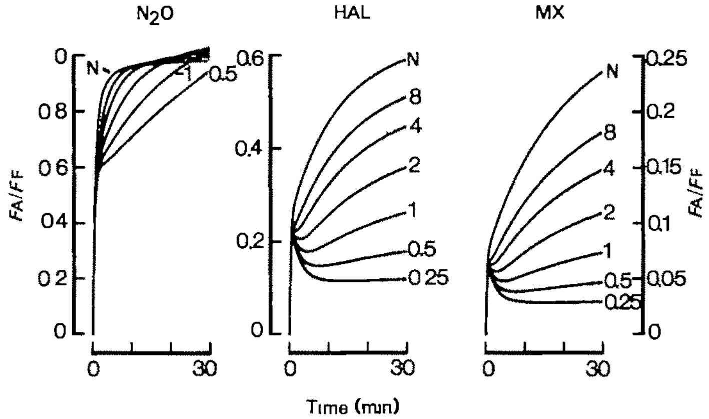

FIG. 4. Alveolar to fresh gas concentration ratios under conditions identical to those detailed for figure 1, except that at the start of each administration the circle system was filled with gas of the same composition as fresh gas.

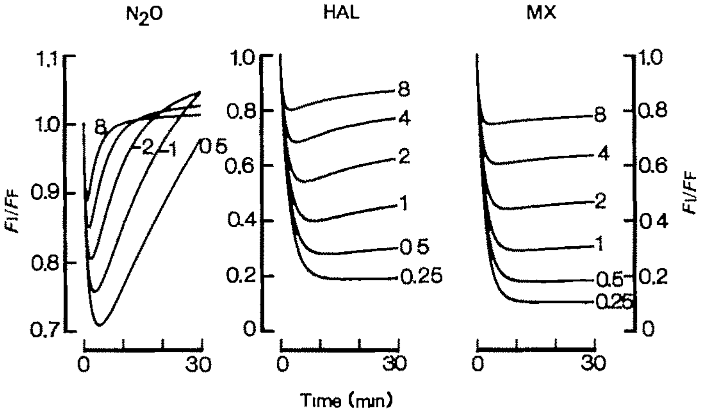

FIG. 5. Inspired to fresh gas concentration ratios during the circle system administrations shown in figure 4.

tion in inspired anaesthetic concentration will decrease the rate of uptake and limit the rate of increase of alveolar concentration. As the fresh gas flow to the circle system is diminished, so removal of anaesthetic by the subject has an increasing effect upon the residual concentration of that agent. With increasing blood solubility of an agent, increasing amounts are removed by uptake by the subject, and the effects of the circle system on gaseous homeostasis are correspondingly increased.

The changes in nitrous oxide concentration in the subject and in the circle system reflect an interplay between the uptake of this agent and oxygen uptake. In the early stages of administration the magnitude of nitrous oxide uptake commonly exceeds the magnitude of oxygen uptake. With the circle system primed with fresh gas, nitrous oxide concentration within the system decreases initially and oxygen concentration increases. Within a relatively short period of time, the rate of nitrous oxide uptake decreases, first to equal and then to be less than oxygen uptake. This explains the later increases in nitrous oxide concentrations shown in figures 4 and 5. If fresh gas composition is unchanged during the administration of nitrous oxide via a circle system, alveolar and inspired nitrous oxide concentrations will always eventually increase to exceed the fresh gas concentration. The final equilibrium under these conditions will be influenced by the fresh gas flow and the magnitude of oxygen uptake. In the examples shown here the inspired nitrous oxide concentration will eventually be slightly greater than the fresh gas concentration with a fresh gas flow of 8 litre min^{-1}. At a maintained fresh gas flow of 0.5 litre min^{-1} of 60% nitrous oxide and with an unchanged oxygen uptake, inspired nitrous oxide concentration would, in theory, (but not in practice) eventually increase to 100%. These factors influencing nitrous oxide concentrations during administration via a circle system are also at play with the other two agents. Because these agents have a far slower time course of uptake than nitrous oxide, are administered with a high concentration of oxygen and have saturated vapour pressures considerably less than 1 atmosphere, it would require a very prolonged administration of a fixed fresh gas flow before inspired and alveolar concentration exceeded fresh gas concentration, and a potentially hypoxic gas mixture could not be present in the circle system. At a fresh gas flow of 0.25 litre min^{-1} of 2% halothane and with the oxygen uptake as shown in table I, it can be predicted that, at equilibrium, inspired anaesthetic concentrations should exceed 14%. It would, however, require many hours of administration for such high inspired concentration to occur with halothane. Because of its low saturated vapour pressure, such a concentration could not occur with methoxyflurane.

Influence of circle system volume

Figures 1–5 demonstrate that the early course of anaesthetic uptake is influenced markedly by the composition of gas initially present within the circle system. A further factor which will influence the course of uptake is the initial volume of the circle system. This influence of circle system volume is illustrated in figures 6 and 7, which show circle system and alveolar anaesthetic concentrations during the use of circle systems of 3- and 12-litre volume and supplied with a fresh gas flow of 1 litre min^{-1}. These figures show the effects of having the system both initially free of agent, and primed with fresh gas. With the system unprimed with agent, circle system and alveolar anaesthetic concentrations increase more rapidly with the circle system of low volume. Conversely, when the system is initially primed with fresh gas, the initial decrease in circle system and alveolar anaesthetic concentrations are greatest with the smaller volume system.

With nitrous oxide delivered to the larger volume circle system initially free of this agent,

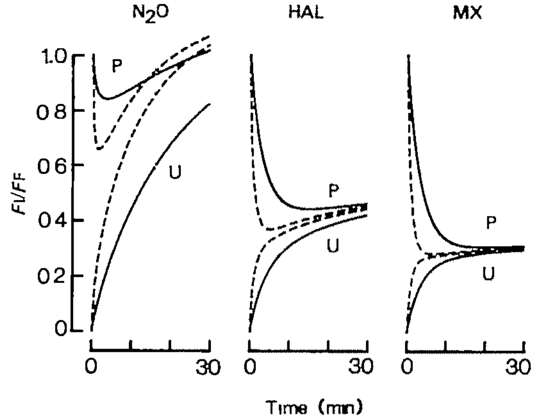

FIG. 6. Inspired to fresh gas concentration ratios during the use of circle systems of 12-litre (continuous curves) and 3-litre (interrupted curves) volumes. The curves marked U which start with a value of zero refer to conditions with the circle system initially unprimed with the agent in use. With the curves marked P the system was initially filled with fresh gas.

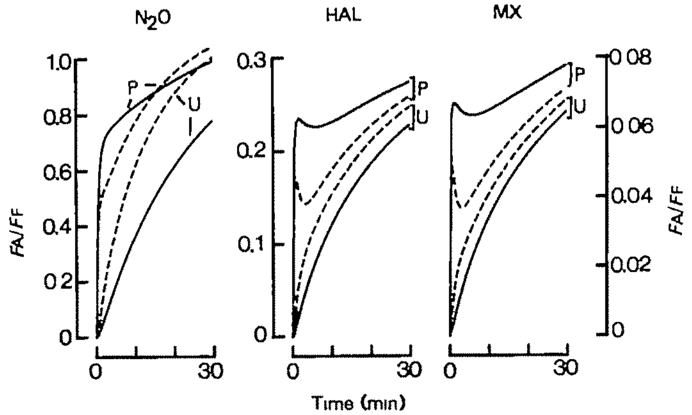

FIG. 7. Alveolar to fresh gas concentration ratios during the use of circle systems of 3- and 12-litre volume detailed in figure 6.

the concentration in the circle system at 30 min is about 80% of the fresh gas concentration. With the smaller volume circle system initially containing oxygen, and with both high and low volume systems when initially containing nitrous oxide, circle system concentrations at 30 min are slightly greater than the fresh gas concentration. With both volatile agents, circle system concentrations are nearly equal at 30 min, regardless of the composition of gas initially present in the circle system, but at a concentration considerably less than that in fresh gas.

Figure 7 shows the alveolar anaesthetic concentrations corresponding to the inspired concentrations of figure 6. As is to be expected, alveolar concentrations increase more rapidly when the system is primed initially with the agent in use. With the system initially free of fresh gas, alveolar concentrations follow a smooth curve, and increase more rapidly with the system of smaller volume. When fresh gas is initially present in the circle system, there is a sharp initial increase in alveolar concentration followed, in the case of the volatile agents, by a sharp decrease. Alveolar concentrations increase to a higher initial peak with the system of larger volume, but this initial rate of increase of alveolar concentration is less well maintained than with the system of smaller volume. In the case of nitrous oxide, and with the system initially primed with fresh gas, alveolar concentrations during use of a system of small volume exceed alveolar concentrations with the larger volume system after about 20 min. These changes reflect the changes in inspired concentrations under these conditions.

The volume of a circle system is large in relation to the magnitude of gas exchange, and may be large in relation to the magnitude of fresh gas flow. This relatively large volume gives the circle system some buffering properties, and reduces the rate at which the composition of gas within the system will change as a result of gas uptake, or a change in fresh gas flow or composition.

In a previous publication (Conway, 1981), the buffering properties were expressed in terms of a time constant of change. The magnitude of this time constant was given by:

$$\text{Time constant} = \frac{\text{Circle system volume}}{\text{Fresh gas flow} - \text{net gas uptake}}$$

where the term net gas uptake refers to the algebraic sum of all gas uptake with the exception of carbon dioxide. In the absence of gas uptake, the time constant reflects the wash-in or wash-out characteristics of the system. Thus with a circle system of 6-litre volume and a fresh gas flow of 8 litre min^{-1}, the time constant is 45 s, whilst with the same circle system volume and a fresh gas flow of 0.25 litre min^{-1} the time constant is 24 min. Removal of gas from the system by uptake effectively diminishes the influence of fresh gas flow upon circle system gas composition and increases the time constant of change, so that (in theory) when fresh gas flow exactly balances uptake, the time constant is infinite.

This definition of a time constant disguises the influence on circle system and alveolar gas composition of ventilation by the subject. It is convenient to consider the volume uptake of inhaled anaesthetic gases as having two related components—gas taken up by solution in blood and body tissues, and gas added to the gas phase of the lung compartment. The quantity of gas taken up by solution will be predominantly influenced by alveolar gas concentration, cardiac output and the solubility of the agent in blood and body tissues. The amount of gas added to or removed from the gas phase of the lungs will depend mainly upon the inspired to alveolar concentration difference, lung volume and ventilation. At the start of the administration of an anaesthetic, addition to the gas phase is the predominant component of gas uptake and, thus, ventilation plays a major role in determining the rate of increase of alveolar concentration. Later in the administration, when alveolar concentration is changing more slowly, uptake by solution will predominate and ventilation will play a lesser role in determining alveolar concentration. It is for this reason that, in figure 4, where the circle system is in use and initially primed with fresh gas, alveolar concentrations of each gas increase in the first few minutes of administration at nearly equal rates regardless of fresh gas flow, and the rates are similar for each of the three gases. The time constant of change here is mainly related to circle system volume and lung volume, and these are the same in all the examples shown. Indeed, for the first few breaths of any of these administrations, the patterns of increase in alveolar concentration are closely identical regardless of whether or not the circle system is in use, and are determined mainly by lung volume and ventilation. After this initial period of mixing of gas within the lung compartment with that in the circle system, uptake by solution by the subject and the magnitude of fresh gas flow come to play a predominant role in determining inspired and, thus, alveoloar gas concentrations.

This early influence of ventilation upon anaesthetic uptake explains why, with a circle system initially primed with agent, alveolar anaesthetic concentrations follow the patterns shown in figure 7. In the first minute of administration the major changes that are occurring relate to gas in the subject's FRC mixing with gas in the circle system. With the circle system initially filled with anaesthetic agent, the amount of agent available to undergo mixing increases as the circle system volume is increased. With a large volume system a higher initial peak value will, therefore, be reached. With a smaller volume system the initial sharp increase in alveolar concentration reaches a lower value and is sustained for a slightly shorter period of time than with the larger volume system. However, following the initial, mainly ventilation-dependent, phase of uptake, the shorter time constant of change of a 3-litre volume circle system results in alveolar concentrations at a more rapid rate than with the 12-litre system.

Concentration and second gas effects

The dependence of the rate of increase of alveolar nitrous oxide concentration upon the fresh gas concentration and the augmentation of these effects when a circle system is in use are illustrated in figure 8. Under non-rebreathing conditions alveolar concentration increases more rapidly towards inspired concentration when 60% nitrous oxide is in use than with 6% nitrous oxide. The difference becomes more marked with a circle system, with increasing augmentation of the effect as fresh gas flow is reduced.

The concentration effect reflects the influence of the initial concentration of a component of a gas mixture upon the effects of removing a proportion of that component from the mixture. If, for instance the nitrous oxide concentration in a nitrous oxide–oxygen mixture is 1%, removal of one-half of the nitrous oxide present reduces nitrous oxide concentration in the mixture to just over one-half of its initial concentration. If the initial nitrous oxide concentration is 50%, then removal of one-half this gas reduces the residual concentration to two-thirds of the initial value, whilst with 100% nitrous oxide, removal of one-half of this gas has no effect upon nitrous oxide concentration.

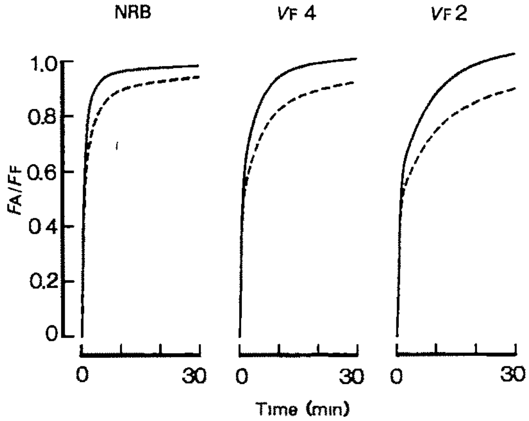

FIG. 8. Alveolar to fresh gas concentration ratios during administration of 60% nitrous oxide (continuous curves) and 6% nitrous oxide (interrupted curves) under non-rebreathing conditions (NRB) and with the circle system supplied with fresh gas flows of 4 ($\dot{V}_F4$) and 2 ($\dot{V}_F2$) litre min^{-1}.

The concentration effect is evident when an agent is used over a wide range of inspired concentrations, and when significant amounts of that agent are taken up by the body. Nitrous oxide is relatively insoluble in blood, but when it is used in an adult subject at an inspired concentration of 60%, uptake in the first few minutes usually exceeds 1 litre min^{-1}, and throughout a 2-h administration its uptake in the body is unlikely to decrease to less than 100 ml min^{-1}. Methoxyflurane, although taken up by the body in comparatively large amounts, is administered over a narrow inspired concentration range and, thus, exhibits an insignificant concentration effect. Halothane occupies an intermediate place between these two agents as regards both its blood solubility and potential inspired concentration range. A small concentration effect could be demonstrated when 10% halothane was administered. Within the conventional range of inspired concentrations, the concentration effect for halothane was negligible.

When a circle system is in use, the concentration effect will operate not only in the alveolar space, but also within the circle system (Conway, 1984). If the fresh gas concentration of an agent is high, removal of an agent by uptake will have a lesser effect upon the residual concentration of that gas within the circle system and thus in the inspired gas, than if fresh gas concentration is low. Because the influence of uptake upon circle system gas composition increases as fresh gas flow decreases, so the magnitude of the concentration effect also increases as fresh gas flow is reduced from high to low values. This influence of fresh gas flow is evident in figure 8.

The second gas effect results from the increase in concentration of one component of a gas mixture caused by removal of part of another component. Like the concentration effect, this phenomenon will influence circle system gas composition as well as acting in the alveolar space, and will have an increasing influence as fresh gas flow is reduced from high to low values. This effect is shown for halothane and nitrous oxide in figure 9. Under non-rebreathing conditions the second gas effect of halothane upon nitrous oxide is hardly discernible. With the circle system in use this effect is slightly more pronounced. Figure 9 shows that the absolute magnitude of the second gas effect of nitrous oxide upon halothane is approximately equal under non-rebreathing conditions and with the circle system in use. As alveolar halothane concentrations are less during circle system use, this implies an increase in the relative magnitude of this effect.

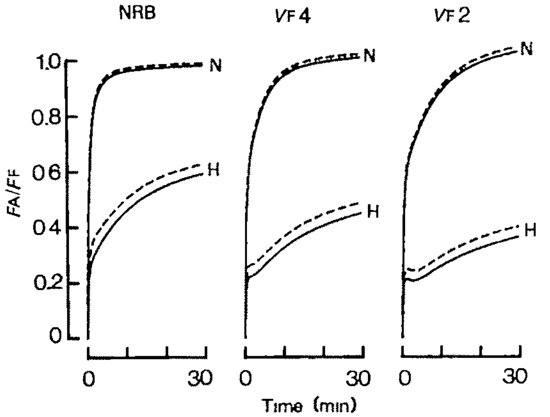

FIG. 9. Alveolar to fresh gas concentration ratios during administration of 60% nitrous oxide (N) and 2% halothane (H) separately (continuous curves) and in combination (interrupted curves) under non-rebreathing conditions (NRB) and with the circle system supplied with fresh gas flows of 4 and 2 litre min^{-1}.

Influence of ventilation and cardiac output upon uptake

The effects of a doubling and halving of cardiac output upon the rates of increase in alveolar anaesthetic concentration, under non-rebreathing conditions and with a circle system supplied with a fresh gas flow 1 litre min^{-1}, are shown in figure 10. The corresponding effects of similar changes in ventilation are shown in figure 11. These

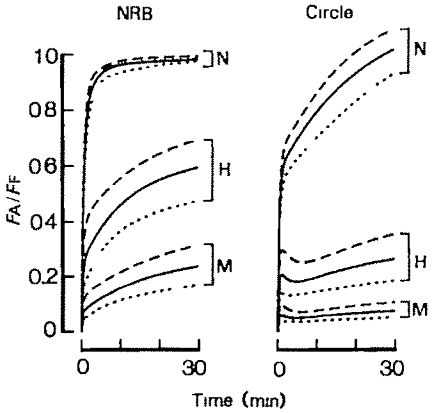

FIG. 10. Alveolar to fresh gas concentration ratios during administration of nitrous oxide (N), halothane (H) and methoxyflurane (M) under non-rebreathing conditions and with a circle system supplied with a fresh gas flow of 1 litre min^{-1}. The continuous lines relate to the model having a cardiac output of 5 litre min^{-1}. The interrupted lines relate to a halving, and the dotted lines to a doubling of cardiac output.

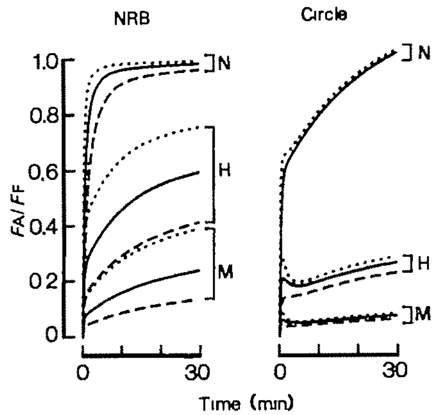

FIG. 11. Alveolar to fresh gas concentration ratios during administration of nitrous oxide (N), halothane (H) and methoxyflurane (M) under non-rebreathing conditions and with a circle system supplied with a fresh gas flow of 1 litre min^{-1}. The continuous lines relate to the model having a minute ventilation of 6 litre min^{-1}. The interrupted lines relate to a halving, and the dotted lines to a doubling of minute ventilation.

effects, together with the effects at different fresh gas flows, are shown as a histogram in figure 12. A decrease in cardiac output results in a lesser amount of agent being removed from the alveolar space by blood perfusing the lung, and the increase in alveolar tension that this produces is associated with a reduced rate of uptake of anaesthetic agent by the subject. An increase in ventilation results in a greater amount of agent being available for uptake from alveolar gas into pulmonary capillary blood, and thus an increase in both the rate of increase in alveolar concentration and the rate of uptake into body tissues. The effects of changes in both cardiac output and ventilation are least with nitrous oxide. Whilst the changes with halothane are larger in the absolute sense than those with methoxyflurane, figure 12 shows that, in terms of percentage change from control, the reverse is true.

The right-hand portion of figure 10 shows the effects of changes in cardiac output during the use of a circle system. It is apparent that, when the circle system is in use, the influences of cardiac output on alveolar nitrous oxide concentration are enhanced. The influences of cardiac output upon the two volatile agents are less obvious, but figure 12 shows that the effect of a circle system is to enhance the influence of cardiac output with all agents. Figure 11 shows that, with a circle system in use, the effects of ventilation on alveolar concentrations of all three gases have been considerably limited.

These effects of a circle system result from changes in circle system, and thus inspired, gas concentration, as a result of the influence of cardiac output and ventilation upon uptake. A

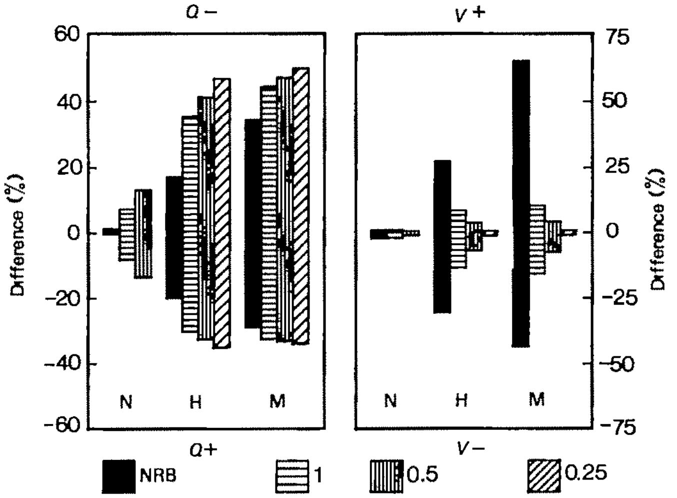

FIG. 12. Histogram to show the effects of doubling and halving cardiac output (left hand panel) and ventilation (right hand panel) upon alveolar anaesthetic concentrations. In this and the succeeding histograms, alveolar concentrations at the end of 30-min administrations for each cardiac output and ventilation value are expressed as the percentage difference from the alveolar concentrations at the end of a 30-min administration with the control values of cardiac output and ventilation. The solid bars refer to the non-rebreathing state, horizontal hatching refers to a fresh gas flow of 1 litre min^{-1}, vertical hatching refers to a fresh gas flow of 0.5 litre min^{-1} and diagonal hatching refers to a fresh gas flow of 0.25 litre min^{-1}.

reduction in cardiac output and the consequent reduced rate of removal of agent from alveolar gas into pulmonary capillary blood will, during circle system use, be associated with a reduced amount of agent being removed from the system. The resulting increased inspired gas concentration will tend further to increase alveolar gas concentration. An increase in ventilation will increase the amount of an agent removed from the system and thus reduce inspired concentration. This will oppose the effects of ventilation upon alveolar concentration. The magnitudes of the augmentation of the effects of changes in cardiac output and the reduction of the effects of changes in ventilation increase as fresh gas flow is reduced towards basal values. This is because removal of a given amount of agent from a circle system will have a greater effect upon the residual concentration when fresh gas flow is low than when it is high.

These modifications, by a circle system, of the effects of ventilation upon the uptake process confirm those which Eger and his associates derived from a simple analogue model (Eger et al., 1973; Eger, 1974). These workers also showed that the use of a circle system augmented the effects on alveolar anaesthetic concentration of changes in uptake by the subject, but did not differentiate between changes in uptake as a result of alterations in cardiac output and those from changes in blood solubility.

Figure 12 shows that the diminution of the effects of changes in ventilation on alveolar gas concentration that occur with the circle system become more marked as the blood solubility of the agent used increases. At a fresh gas flow of 0.5 litre min^{-1}, a doubling of ventilation has, in the case of nitrous oxide, an effect which is 63% of the effect seen under non-rebreathing conditions. The corresponding figures for halothane and methoxyflurane are 14% and 6.5%, respectively. Conversely, with a circle system in use, the augmentation of the effects of changes in cardiac output on alveolar anaesthetic concentration is greater with agents of low as opposed to high blood solubility. At a fresh gas flow of 0.5 litre min^{-1} the effect of halving cardiac output is, in the case of nitrous oxide, more than 12 times the effect under non-rebreathing conditions. With halothane the effect is 140% greater, and with methoxyflurane only 40% greater than in the non-rebreathing state. Whilst under non-rebreathing conditions the effects of changes in both cardiac output and ventilation on alveolar gas concentration are approximately twice as great for methoxyflurane as for halothane, with the circle system supplied with a fresh gas flow of 0.5 and 0.25 litre min^{-1} the influences of both these variables on the two agents are approximately equal. Indeed, at the lowest fresh gas flows, the effects of doubling or halving ventilation upon alveolar concentrations of all three agents used are slight and of the same order of magnitude.

These modifications by a circle system of the effects of changes in ventilation and cardiac output upon the uptake process reflect the interrelationships between inspired gas composition and gas uptake inherent in the use of a circle system. Use of a circle system will augment the effects of a decrease in cardiac output because of a concomitant increase in circle system, and thus inspired, gas concentration. This increase will tend to promote uptake and oppose the primary influence of the reduction in cardiac output. The opposing influence will be greater with agents of high blood solubility which are taken up in large rather than small amounts, and will have a greater influence as the flow of fresh gas is reduced from high to low. Limitation of the effects of ventilation results from a reduction in inspired anaesthetic concentration. The degree of attenuation of the effects of an increase in ventilation will depend on the amount of agent removed from the circle system, and this amount will again be greater with agents of high rather than low blood solubility. The effect of the removal of the agent on gas concentrations in the circle system will increase as fresh gas flow is reduced from high to low. Similar reasoning can be used to explain the effects, during the use of the circle system, of reductions in ventilation and increases in cardiac output.

These effects of changes in ventilation during the use of the circle system differ from the effects of changes in ventilation on the depth of anaesthesia that occur when a vaporizer is used within a circle system. In the studies described here, vaporization of volatile agents has been performed outside the circle system and is uninfluenced by ventilation. With a vaporizer within the system, ventilation would be the major determinant of vaporization and, thus, of the composition of the inspired and alveolar gases.

The reduced influence of ventilation shown here also differs from the situation that arises when, during circle system use, a constant alveolar anaesthetic concentration is maintained by manipulation of the amount of anaesthetic added to the system and, hence, of the inspired gas concentration. Under these conditions the amount of agent present in the alveolar space remains constant, and the uptake of the agent by solution in the blood perfusing the lung is controlled by the amount of agent added to the lungs in the inspired gas—the product of inspired concentration and alveolar ventilation. If this control is effected purely by manipulation of the inspired gas concentration, changes in ventilation will be compensated for by the changes in the inspired concentration and will not influence the uptake of the anaesthetic.

In evaluating the effects of cardiac output and ventilation, changes in alveolar gas concentration have been compared at the end of 30-min periods of administration. This is a convenient but arbitrary criterion. It is not completely satisfactory to use this criterion in comparing the effects of blood flow and ventilation on nitrous oxide with those on the two volatile agents, as with nitrous oxide there is a more rapid increase in alveolar towards the equilibrium concentration. Cardiac output and ventilation will influence the rate of increase of alveolar gas concentration, but will not influence the final equilibrium concentration. The effects of cardiac output and ventilation on the uptake process will diminish as equilibrium is approached. The criterion used here has been chosen to illustrate qualitative differences of the effects of cardiac output and ventilation on the three agents used, and is not intended as a quantitative index of these differences.

Nitrous oxide has been used in these studies at a much higher concentration than the two volatile agents. Figure 13 compares the effects of changes in cardiac output and ventilation when nitrous oxide is supplied at fresh gas concentrations of 60% and 2%, under non-rebreathing conditions and with fresh gas flows to the circle system of 1 and 0.5 litre min^{-1}. This figure shows that, both under non-rebreathing conditions and with a circle system, the effects of cardiac output and ventilation on alveolar anaesthetic concentrations are concentration-dependent, being greater when 2% nitrous oxide is being administered than with 60% nitrous oxide. This influence of administered gas concentration on the effects of cardiac output and ventilation can be explained in a way similar to the concentration effect. If the alveolar concentration of a gas is 100%, it will not be influenced by changes in cardiac output and ventilation. As alveolar concentration is reduced, so alterations in the amount of gas removed by uptake have an increasing influence on the residual gas concentration.

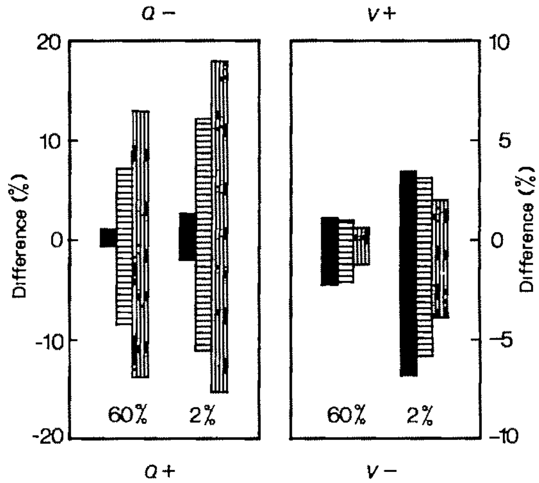

FIG. 13. Histogram to show the effects of doubling and halving cardiac output and ventilation during administration of 60% and 2% nitrous oxide. Results are expressed as in figure 12, and the hatching as is for that figure.

Similar effects take place within the circle system, so that the influence of factors modifying uptake will increase as fresh gas concentration is reduced.

Given that the magnitude of the influences of cardiac output and ventilation upon alveolar anaesthetic concentrations are influenced by the alveolar concentration of an agent, it can be predicted that, because of the second gas effect, cardiac output and ventilation will have a slightly lesser effect on alveolar anaesthetic concentrations when agents are given in combination than when given separately. That this is so is shown in figure 14, which compares the influences of cardiac output and ventilation on alveolar halothane concentration when 2% halothane is administered with oxygen, and with 60% nitrous oxide. Both under non-rebreathing conditions and with the circle system in use, the influences of cardiac output and ventilation are greater when halothane is being given with oxygen than when nitrous oxide is present, although the differences are less than those seen with high and low concentrations of nitrous oxide.

CONCLUSIONS

As stated previously, the patterns of fresh gas flow and composition used in these studies have not been intended to follow those used during clinical

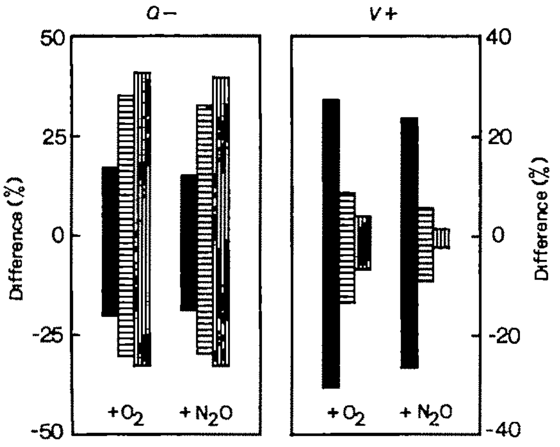

FIG. 14. Histogram to show the effects of doubling and halving cardiac output and ventilation during the administration of 2% halothane in oxygen (+O_2) and in 60% nitrous oxide (+N_2O). The method of expressing results and the hatching are as for figure 12.

anaesthesia, but have been rigidly controlled so as to demonstrate the various aspects of the uptake of anaesthetic gases that are influenced by the use of a circle system. The findings relate to the behaviour of a mathematical model, and should be taken as a guide to the pattern of anaesthetic uptake and, thus, the course of anaesthesia when the circle system is in use, rather than as predictions of absolute behaviour. In these studies the influence of nitrogen has been ignored. In practice, nitrogen initially present in the lungs and tissues of the subject would dilute the contents of the circle system, and slow down the course of anaesthetic uptake. This effect would be slight except at fresh gas flows close to the basal value.

The only direct way in which the presence of a circle system can influence gas uptake is by a modification of the inspired gas concentration. Because gas concentration within a circle system is itself influenced by the uptake of gas by the subject, there are complex interrelations between fresh gas flow and composition, inspired and alveolar gas concentration, and the uptake of gas by the subject. The effects of factors known to alter the course of uptake, such as changes in ventilation and cardiac output, may be influenced considerably by these interrelations.

Of the three agents chosen to illustrate the findings of this paper nitrous oxide was the least, and methoxyflurane the most affected by the presence of a circle system. The effects on halothane, a gas of intermediate blood solubility, were of intermediate magnitude.

Halothane, enflurane and isoflurane are the most widely used volatile anaesthetic agents. The performance of the model with these last two agents in the studies described in this paper is broadly similar to that of halothane. A major reason for the popularity of these agents is their relatively low solubility in blood. When these agents are used under non-rebreathing conditions an adequate depth of anaesthesia can be attained fairly rapidly, and can be controlled readily by adjusting the inspired concentration. When these agents are used with a circle system and a low fresh gas flow, this does not apply. The alveolar concentration of the anaesthetic will now increase towards the fresh gas concentration in a manner more closely resembling that seen with highly blood soluble agents. With a circle system used in the ways used in this study, attainment of adequate brain concentrations of volatile agents would be a lengthy process, and changes in the fresh gas anaesthetic concentration would take a considerable time to influence the depth of anaesthesia. In practice, the administrator has to take steps to overcome this debasement, such as priming the system with a high concentration of anaesthetic agent, commencing administration with a period of high fresh gas flow, or increasing fresh gas flow at times when it is necessary to alter the depth of anaesthesia.

The paradoxical concentration and second gas dependence of the effects of cardiac output and ventilation on gas uptake is unlikely to be of major clinical significance. The overall influence of a circle system in augmenting the effects of changes in cardiac output and limiting the effects of changes in ventilation is of some importance and, in one way, can be seen as a potential disadvantage of circle systems. In the studies described, cardiac output and ventilation were maintained constant throughout each study. In clinical practice cardiac output will tend to decrease as the depth of anaesthesia increases and, in spontaneously breathing subjects, this reduction in cardiac output will commonly be associated with a decrease in ventilation. A decrease in cardiac output will result in a greater increase in alveolar anaesthetic concentration when a circle is in use than under non-rebreathing conditions, and the increased depth of anaesthesia will tend to reduce cardiac output further. Since the effects of a decrease in ventilation are attenuated when a circle system is in use, these potentially progressive effects of cardiac output would not be opposed by any coexistent respiratory depression.

ACKNOWLEDGEMENT

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A VENTILATOR FOR USE IN NUCLEAR MAGNETIC RESONANCE STUDIES

J. G. RAMSAY, L. GALE AND M. K. SYKES

The major problem encountered when ventilating small animals situated within the magnet of a nuclear resonance (NMR) machine is that most ventilators suitable for use in animals (and man) contain ferromagnetic components, and cannot be placed close to the magnet. If the ventilator is situated at some distance from the animal, long connecting tubes must be used. These result in an increase in the volume of gas compressed and an unacceptable variation in delivered tidal volume when there are changes in total thoracic compliance or airway resistance. A reduction in the compressed gas volume can be achieved by decreasing the diameter of the tubes but, since this increases the resistance to expiratory gas flow, lung volume is increased and cardiac output decreased. To overcome these problems, we have designed a breathing system which permits the ventilator to be situated at a distance of several metres from the animal, but has minimal compressed gas volume and negligible expiratory flow resistance. The system is suitable for the ventilation of small animals, such as rats and rabbits, and would also prove useful when it is necessary to ventilate the animal in a hazardous environment, for example, during exposure to x-rays.

MATERIALS AND METHODS

Description

The ventilator is essentially a T-piece occluder with minimal internal compliance (fig. 1). With this system, tidal volume is governed by the frequency of ventilation, duration of inspiration, and fresh gas flow. Fresh gases are supplied from a standard anaesthetic machine rotameter block at

SUMMARY

The problem of ventilating small animals during nuclear magnetic resonance studies has been solved by using a T-piece system with a remotely controlled non-magnetic expiratory valve. This system does not affect the NMR signal, has minimal internal compliance and expiratory resistance, permits accurate control of peak airway pressure, and may be of use when animals have to be ventilated in hazardous surroundings.

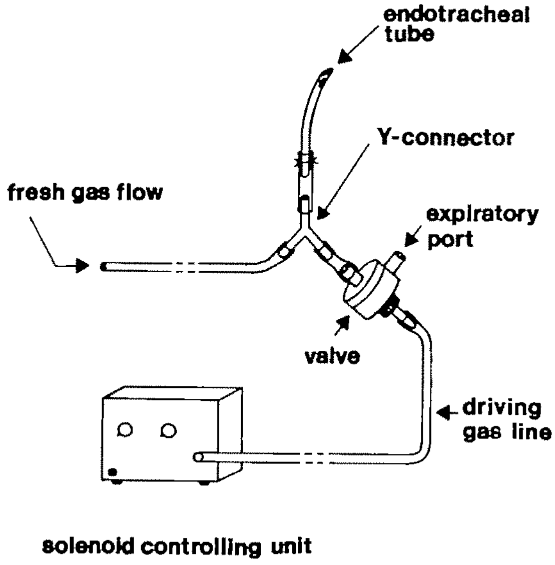

FIG. 1. The ventilator circuit, including the valve and its controlling unit. The valve is entirely non-metallic and acts as a remotely controlled T-piece occluder.

J. G. RAMSAY,* B.SC., M.D., F.R.C.P.(C).; L. GALE; M. K. SYKES, M.A., M.B. B.CHIR., F.F.A.R.C.S., F.F.A.R.A.C.S. (HON.); Nuffield Department of Anaesthetics, University of Oxford, The Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.

* Present address: Department of Anaesthesia, Royal Victoria Hospital, Room S505, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

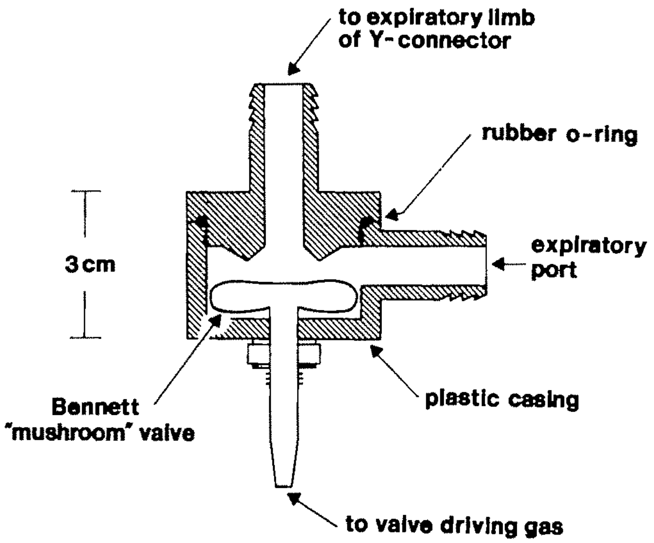

FIG. 2. Scale drawing (cross section) of the valve in the deflated (expiratory) position. Inflation of the mushroom valve by the valve driving gas occludes the expiratory limb of the Y-connector during inspiration.

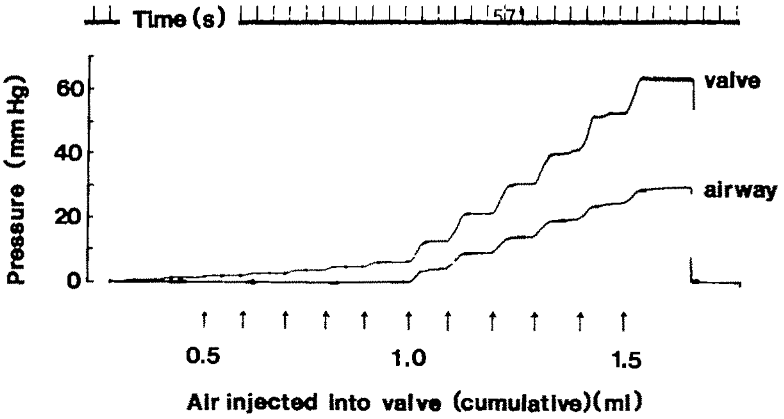

FIG. 3. Simultaneous recording of airway and mushroom valve ("driving") pressures as a fresh gas flow of 0.75 litre min^{-1} is directed through the valve, and 0.1-ml increments of air are injected to the mushroom valve. Note that the valve first becomes occlusive at 1 ml, and that to obtain a given airway pressure, a much higher pressure (approximately double) must be generated inside the mushroom valve.

a pressure of 400 kPa and transmitted to the Y-connector and tracheal tube through 6 m of rigid polyethylene tubing with an internal diameter of 3 mm (Automatic Valve Systems Ltd, Market Bosworth, Nuneaton). The expiratory limb of the Y-connector is connected directly to the expiratory valve assembly with a short length of wide-bore tubing. Gases are then ducted from the expiratory port to an active or passive anti-pollution gas scavenging system.

The expiratory valve consists of the diaphragm assembly ("mushroom" valve) from the Bennett PR-2 Ventilator (part no. 2649, Puritan Bennett International Corp., Chichester, West Sussex) mounted in a plastic casing (fig. 2). The resting state of the valve is in the expiratory (deflated) position, and it is inflated during the inspiratory phase by gas from a separate low pressure source. The pressure of this gas is adjusted by a Norgren model R.O.6 regulator (I.M.I. Norgren, Shipston on Stour, Warwickshire), to a value which maintains occlusion of the expiratory valve up to the peak inspiratory pressure desired, but allows leak past the valve at higher values (fig. 3). Thus the expiratory valve also acts as a safety blow-off. For additional safety, an Oxford Ventilator pressure relief valve (Penlon Ltd, Radley Road, Abingdon, Oxfordshire) is incorporated to the driving gas line. The duration of valve occlusion is controlled by an electronic circuit, which actuates a solenoid valve (Sirai 1.6-mm bore 3-way solenoid valve, normally closed; Alpha Controls Ltd, The Ridgeway Estate, Iver, Buckinghamshire). Since the balloon requires only 1 or 2 ml for occlusive inflation (depending on the airway pressure), the tubing connecting the balloon and solenoid valve can be of 3-mm bore, and at least 6 m in length, without appreciably delaying balloon emptying at the onset of expiration.

Performance tests

The characteristics of this ventilator predicted from the design are that it should function as a time-cycled constant flow generator. Thus tidal volume should be governed by the fresh-gas flow rate and the duration of inspiration, as long as the peak airway pressure does not exceed the blow-off pressure of the expiratory valve. In order to ensure that these characteristics were not modified by the compression of gases within the breathing system, or by a high resistance to gas flow, we performed two studies to define the performance which would be expected when the system was used with small animals such as rats or rabbits.

Internal compliance of the ventilator. To verify that the internal compliance of the circuit was small, the tidal volume was measured with normal and increased airway resistances. The complete circuit as illustrated in figure 1 was attached to a model lung (compliance 3 ml/cm H_2O) via a 3.5-mm i.d. plastic tracheal tube. A variable orifice resistance situated between the Y-connector and the tracheal tube was used to increase airway pressure. The airway pressure and the "lung" pressure (inside the model compliance) were recorded using Statham pressure transducers, and flow was recorded with a Fleisch pneumotachograph and Validyne transducer placed distal to the resistance but proximal to the tracheal tube. Three-millimetre i.d. non-compliant tubing 5 m in length was used for both the fresh gas and the driving gas lines, and the ventilator was set at 30 b.p.m. with an I:E ratio of 1:2, using a fresh gas

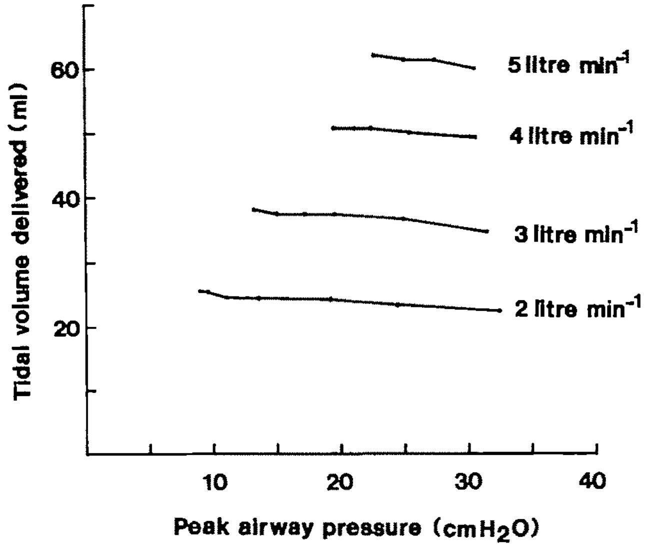

FIG. 4. Delivered tidal volume plotted as a function of peak airway pressure using a 3.5-mm tracheal tube and model lung compliance (3 ml/cm H_2O), as fresh gas flows of 2–5 litre min^{-1}. Airway resistance was altered using an in-series variable orifice resistor, while frequency (30 b.p.m.) and I:E ratio (1:2) were unchanged. There is very little reduction in tidal volume up to the airway pressure at which the valve was set to "blow off", indicating minimal internal compliance.

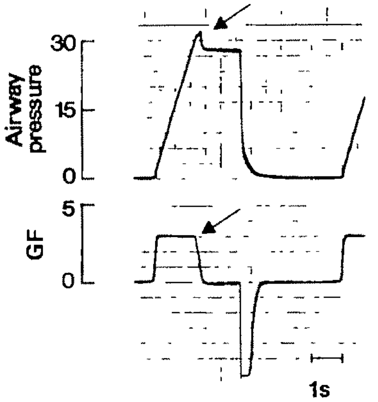

FIG. 5 "Blow off" via the expiratory valve, indicated by abrupt decrease in airway pressure and cessation of inspiratory gas flow (arrows). GF = Gas flow to lungs.

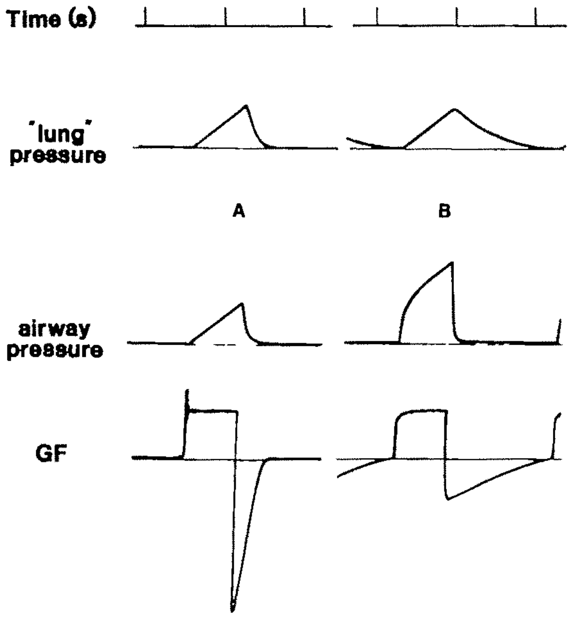

FIG. 6. Characteristic waveforms of "lung" and airway pressures, and flow at normal (A) and increased (B) airway resistance. Note the maintenance of tidal volume (indicated by the same peak "lung" pressure) and inspiratory flow at the increased airway resistance, and the marked reduction in rate of expiratory flow. GF = Gas flow.

flow of 2–5 litre min^{-1} (the settings used for rabbits).

Resistance to expired gas flow. Continuous gas flows between 1 and 15 litre min^{-1} were passed through the expiratory valve and the airway pressure on the patient side of the valve recorded with the Statham pressure transducer.

RESULTS

Internal compliance

Figure 4 illustrates that there was minimal decrease in delivered tidal volume, despite increases in airway pressure produced by increases in airway resistance. The expiratory valve was set to be occlusive up to pressures of 32 cm H_2O and prevented further increases in airway pressure (fig. 5). Figure 6 illustrates characteristic waveforms observed at normal and increased airway resistance, at a fresh gas flow of 3 litre min^{-1}.

Resistance to expired gas flow

There was no change in airway pressure at flows between 1 and 15 litre min^{-1}, indicating no detectable resistance to expired gas flow.

DISCUSSION

The major disadvantage of a T-piece system is that, with an I:E ratio of 1:2, only one-third of the fresh gas flow is used to ventilate the lungs. It is, therefore, uneconomical to use such a ventilator with large animals. At high fresh-gas flows, the Y-connector should be replaced by a T-connector, since the kinetic energy of the fresh gas flow passing through the inspiratory limb of the Y-piece opposes expiratory gas flow from the tracheal tube and so creates a positive end-expiratory pressure which increases lung volume and decreases cardiac output.

With these limitations, the ventilator has proved to be easy to use, reliable and simple to understand. Construction of the valve housing and the electrical circuitry (circuit diagram available from L. Gale) which controls its function is relatively simple. The apparatus described has been in use for several months to ventilate rabbits and rats with halothane in air or oxygen, and there has been no sign of deterioration in the mushroom valve. Tests have also shown that the presence of the plastic valve and tubing does not affect the quality of the results obtained with the NMR machine. The provision of a low internal compliance, low resistance system with adjustable pressure limit has eliminated all the major problems associated with the ventilation of small animals in such situations, and a similar system could be used in many other experimental situations where it is convenient to separate the animal from the main ventilator mechanism.

ACKNOWLEDGEMENT

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AN END-TIDAL SAMPLER FOR USE WITH SLOW RESPONSE ANALYSERS DURING ANAESTHESIA

K. ALAGESAN AND J. F. NUNN

Many gas analysers have a response time which is too slow to permit breath-by-breath analysis at the respiratory frequencies encountered, during anaesthesia, in spontaneously breathing patients. We have examined the feasibility of using an end-tidal sampler to extend the scope of such analysers. The design which we adopted finally follows closely that of Henderson and Haggard (1925), the principle of which was also used by Rahn and Otis (1949) and Severinghaus and Hamilton (1970). Our version is intended for use during spontaneous ventilation and may be assembled entirely from standard parts which are readily available.

MATERIALS AND METHODS

Materials

In the first series of experiments the increase in pressure in the Mapleson A system (Mapleson, 1954) at the end of expiration was used to drive gas directly into the analyser by way of a narrow catheter passed down the bore of the tracheal tube to its lower end. The diameter of the catheter was varied between 0.5 and 1.7 mm i.d. and the end-expiratory pressure between 1 and 4 cm H_2O. The performance of this device with anaesthetized patients was assessed by capnography, using the "breathe-through" cell of the Hewlett–Packard model 47210A capnometer. Continuous recordings of carbon dioxide tension were obtained alternately by (1) passing gas passively through the cell in the manner described above and (2) conventional rapid analysis of gas with the same "breathe-through" cell interposed between the tracheal tube and the catheter mount.

In a second series of experiments we developed a circuit based on a valvular non-rebreathing system (fig. 1). During expiration, deadspace gas is swept past the expiratory valve (fig. 1, top diagram) and, at the end of expiration, end-tidal gas will be located on the distal side of the expiratory valve. Then during inspiration (fig. 1, lower diagram) end-tidal gas may be sampled through the cell of an analyser by utilizing the sub-atmospheric pressure generated in the patient's airway. Reverse flow through the cell during exhalation is prevented by a small check valve, D.

Opening of valve D during inspiration requires the development of a significant sub-atmospheric pressure in the airway—which is 2 cm H_2O in our apparatus. This may be achieved either by loading the inspiratory valve B so that its opening pressure is greater than that of valve D or, alternatively, by holding the inspiratory reservoir at a slight sub-

SUMMARY

An end-tidal sampler is described which can be used during anaesthesia with spontaneous respiration at rates of at least 60 b.p.m. It can be used with slow response analysers such as refractometers and fuel cells to indicate end-tidal concentrations. It can also be used to extend the scope of those breath-to-breath analysers which have a response time which is too slow for the respiratory rates which may occur during anaesthesia with spontaneous breathing. Using the device, mean P_{CO_2} *of the samples was 0.13 kPa less than the corresponding values for the end-expiratory* P_{CO_2} *measured by conventional breath-by-breath analysis. Full response was achieved in 12 breaths.*

K. ALAGESAN,* M.B.B.S., F.F.A.R.C.S., Department of Anaesthesia, Northwick Park Hospital, Watford Road, Harrow HA1 3UJ. J. F. NUNN, M.D., PH.D., F.R.C.S., F.F.A.R.C.S., F.F.A.R.A.C.S.(HON.), F.F.A.R.C.S.I.(HON.), Clinical Research Centre, Watford Road, Harrow HA1 3UJ.

*Present address: Department of Anaesthesia, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.

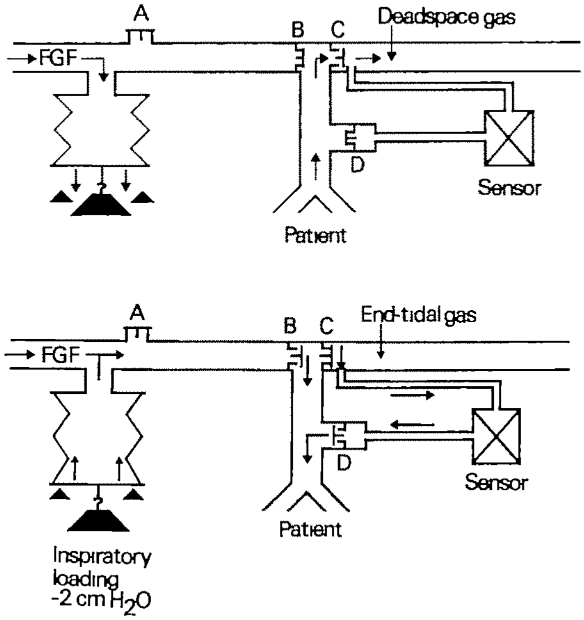

FIG. 1. Circuit of the end-tidal sampler: Top = during early expiration; below = during early inspiration. Valve A is a pressure relief valve with a lower opening pressure than valve B. Valves B and C are low resistance one-way flap valves (Medic-Aid). Valve D is an input check valve type 2-1019 (De Vilbiss). Connections to the sensor are 1.7 mm manometer lines (Portex).

atmospheric pressure, and this we found to be most conveniently achieved with the weighted bellows of Hewlett's "Mandatory Minute Volume (MMV)" apparatus (Hewlett, Platt and Terry, 1977). Excess fresh gas was vented to atmosphere through valve A which had a lower opening pressure than valve B.

It is essential to prevent overfilling of the reservoir, which would cause excess fresh gas to pass into the expiratory limb via valves B and C and so contaminate the end-tidal gas. This can be achieved either by adjusting the fresh gas flow continuously to equal the patient's minute volume or alternatively by using the bellows from Hewlett's MMV apparatus which automatically vents the excess fresh gas to the atmosphere when the bellows is expanded fully.

Validation

Measurements of $P\mathrm{CO}_2$ *in volunteers.* Volunteers were asked to breathe through the system, with oxygen as fresh gas, at respiratory rates varying from 10 to 60 b.p.m. The Hewlett–Packard capnometer was used to measure the end-tidal $P\mathrm{CO}_2$, the breathe-through sensor being placed alternately in series with the end-tidal sampler (volume 7.5 ml) and between the mouth piece and the system. The internal standard was used for calibration. We compared the mean of six breaths before and six breaths after the sampling period with the mean of the end-tidal sample after 12 breaths when the partial pressure of carbon dioxide in the sampler had reached a plateau.

Measurements of $P\mathrm{CO}_2$ *and anaesthetic vapour concentrations in anaesthetized patients.* Healthy adults (ASA class 1 and 2) undergoing surgery for varicose veins were studied. Anaesthesia was induced with 2.5% thiopentone followed by suxamethonium 1 mg kg^{-1} i.v., and the trachea was intubated with a cuffed orotracheal tube. Ventilation was assisted manually until spontaneous breathing returned. The patients breathed a mixture of 70% nitrous oxide and halothane in oxygen. The system and capnograph were used as described above. The effect of negative pressure inspiratory loading on breathing was determined by intermittently removing the weight on the bellows.

A mass spectrometer (Medishield Multigas Monitor MS2), tuned to the volatile inhalation anaesthetic in use was used with its probe alternating between the end-tidal sampler and the tracheal tube. The sensor of an Engstron EMMA was placed in series with the sampler. The two mass spectrometer readings were compared with the reading on the EMMA, both instruments being calibrated with a standard gas mixture prepared by pressure dilution and verified using gas chromatography against a volumetric standard. The zero reading of the EMMA was set with 70% nitrous oxide in oxygen, saturated with water vapour at 34 °C.

The water vapour artefact of the EMMA. Awake volunteers breathed through the system with medical air as fresh gas. The EMMA sensor was then placed in series with the end-tidal sampler and the output from the EMMA displayed on a strip chart recorder. Each subject breathed for 1 h continuously and the selector switch on the EMMA was turned to select halothane, isoflurane and enflurane in rotation every 5 min.

Volume of the sampler. Volume of the end-tidal sampler was measured by water displacement.

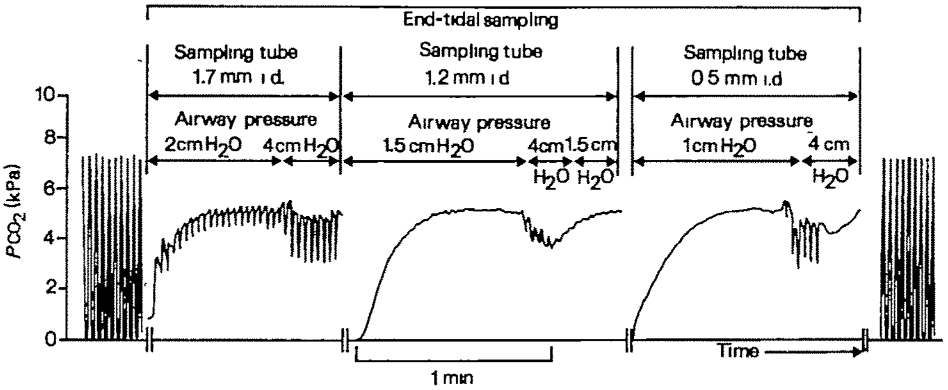

FIG. 2. Typical infra-red P_{CO_2} tracing of an anaesthetized patient breathing spontaneously and using end-expiratory pressure for spontaneous delivery of an end-tidal sample from a tube with its tip near the carina. Peak end-expiratory airway pressure is shown. Conventional breath-by-breath records are shown at the beginning and end of the trace. It was impossible to obtain a representative end-tidal sample by this technique.

Response time using volunteers. The system was used as in figure 1 except that the inlet to the end-tidal sampler was disconnected from the expiratory tubing and connected to a reservoir containing 2% halothane. The sensor of the EMMA was in series with the end-tidal sampler and the subjects breathed medical air. The time taken for equilibration of the end-tidal sampler with the reservoir of 2% halothane was determined from the output of the EMMA which was displayed on a chart recorder.

RESULTS

In the first series of experiments in which the end-tidal gas was sampled passively by the increase in pressure at the end of expiration in the Mapleson A circuit, the carbon dioxide concentration of the sampled gas was always considerably less than the end-tidal plateau. A typical trace is presented in figure 2. Increasing the opening pressure of the relief valve and decreasing the diameter of the sampling catheter to 0.5 mm i.d. did not result in any significant improvement, and this approach was abandoned.

The following results all refer to the device illustrated in figure 1.

Measurements of P_{CO_2} *in volunteers*

A typical recording is shown in figure 3. Mean values of P_{CO_2} by the end-tidal sampler ranged from 0.08 to 0.13 kPa less than P_{CO_2} by breath-by-breath analysis at frequencies up to 60 b.p.m. (table I). Although small, the differences were significant by Student's *t* test at 11 and 30 b.p.m.

TABLE I. *Comparison of mean end-tidal* P_{CO_2} *(kPa) (SD) measured by rapid breath-by-breath analysis, and by use of the end-tidal sampler, at different respiratory frequencies in a conscious volunteer.* *$P < 0.05$; **$P < 0.01$

	End-tidal P_{CO_2}	
Respiratory frequency (b.p.m.)	Breath-by-breath analysis	End-tidal sampler
11	5.27 (0.13) ($n = 15$)	5.17 (0.10)* ($n = 11$)
30	5.00 (0.18) ($n = 14$)	4.87 (0.09)** ($n = 11$)
60	4.41 (0.42) ($n = 17$)	4.33 (0.38) (NS) ($n = 8$)

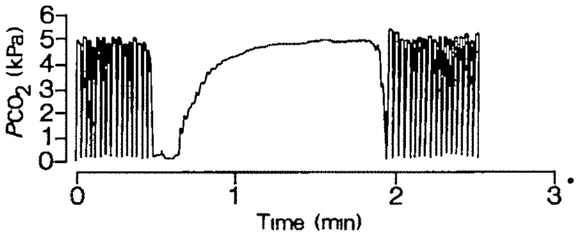

FIG. 3. Typical infra-red P_{CO_2} in a conscious volunteer. The beginning and end of the trace show conventional breath-by-breath analysis while the centre section shows the P_{CO_2} in the end-tidal sampler which was connected at 40 s.

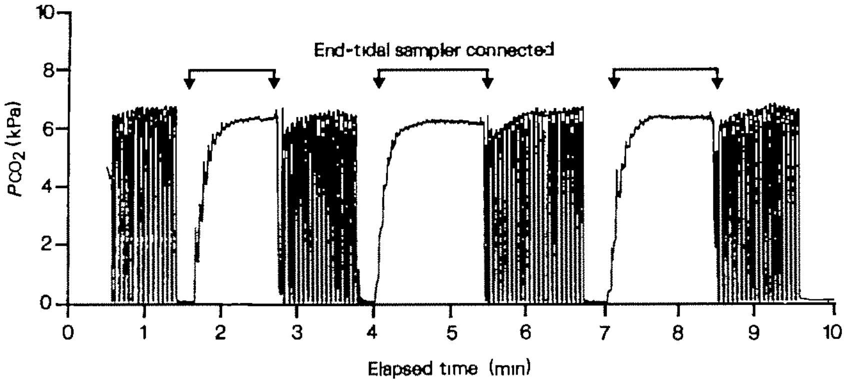

FIG. 4. Typical infra-red P_{CO_2} tracing in an anaesthetized patient breathing spontaneously. Three periods are shown in which the P_{CO_2} sensor was attached to the end-tidal sampler. In between are periods of conventional breath-by-breath analysis.

TABLE II. *Comparison of mean end-tidal* P_{CO_2} *(kPa) (SD) in three patients measured by rapid breath-by-breath analysis and by use of the end-tidal sampler during anaesthesia.* **$P < 0.01$

	End-tidal P_{CO_2}	
Respiratory frequency (b.p.m.)	Breath-by-breath analysis	End-tidal sampler
18	6.59 (0.21) ($n = 12$)	6.63 (0.07) (ns) ($n = 6$)
20	6.63 (0.11) ($n = 12$)	6.44 (0.07)** ($n = 6$)
18	6.76 (0.23) ($n = 12$)	6.51 (0.05)** ($n = 6$)

Measurements of P_{CO_2} *and anaesthetic vapour concentrations in anaesthetized patients*

A typical recording is shown in figure 4. Comparisons of P_{CO_2} by the two methods are shown for three patients in table II. Although the differences were small, they were significant in two instances. The introduction of a sub-atmospheric pressure of 2 cm H_2O did not change the end-tidal carbon dioxide concentration in the patient.

There was no clinically significant difference between the end-tidal halothane concentration measured with the mass spectrometer by rapid breath-by-breath analysis and by means of the sampler (table III). However, use of the EMMA with the end-tidal sampler gave more variable results.

The water vapour artefact of the EMMA

When sampling was performed through the EMMA from awake volunteers, water vapour produced a positive reading depending on the gain setting of the EMMA. Steady readings attained after 11 min were 0.5%, 0.9% and 0.6% when the selector switch was set for halothane, isoflurane and enflurane, respectively, and did not change further during the 1 h study. The humidity of the gas entering the sampler was saturated at 34 °C, but the temperature inside the EMMA sensor was 50 °C, which would result in a relative humidity of about 50%.

Volume of the end-tidal sampler

The total volume of the end-tidal sampler with the sensor of the EMMA in series was 20.4 ml. The individual components and their volumes are given in table IV. Sampled volume was dependent on inspiratory duration as the flow was constant at the sub-atmospheric pressure of 2 cm H_2O and varied from 2 to 6 ml per breath.

Response time

Six breath cycles were required to bring the gas sampler to 90% equilibration with the reservoir of 2% halothane. This accords closely with the rate of equilibration of carbon dioxide shown in figures 3 and 4. We ignored the first 12 breaths in comparing the end-tidal sampler with breath-by-breath analysis as described above.

TABLE III. *End-tidal halothane concentration (%) measured with the end-tidal sampler using both mass spectrometer and EMMA compared with the value determined by rapid breath-by-breath analysis (mass spectrometer)*

Patient	Breath-by-breath analysis by mass spectrometer	Previous column minus end-tidal sample (mass spectrometer)	Previous column minus end-tidal sample (EMMA)
1	0.51	0	0.07
	0.56	0.03	0.07
	0.47	0.02	0.07
	0.55	0.02	0.07
	0.54	0.02	0.07
2	1.25	0	0.05
	1.15	0.05	−0.05
	1.20	0.05	−0.05
	1.15	0.10	−0.10
3	0.70	−0.04	−0.02
	0.54	−0.02	−0.02

TABLE IV. *Volume of the end-tidal sampler with the sensor of the EMMA in series*

	Volume (ml)
Portex 30-cm manometer line ×2	1.4
Connectors ×3	6.0
EMMA sensor	13.0
Total	20.4

DISCUSSION

The failure of the simple device, in which sampling was based on the spontaneous increase in end-expiratory pressure in the Mapleson A circuit, may possibly be explained by the tip of the sampling tube lying to the side of the axial stream of alveolar gas. However, the results of the capnography indicate that the end-tidal sampler illustrated in figure 1 collects end-tidal gas with negligible contamination by inspired gas. It can be used for end-tidal measurements with respiratory frequences up to at least 60 b.p.m. The small difference in end-tidal $P\mathrm{CO}_2$ in table II and figure 4 may, in part, be the result of the extra deadspace (7.5 ml) of the breathe-through cuvette causing an increase in alveolar $P\mathrm{CO}_2$. We did not encounter obstruction of the connections to the sampler but, should this occur, there would be a fixed reading from the last sample before obstruction occurred.

The major problem which we encountered was not caused by the sampler but by the water vapour artefact of the EMMA. We have confirmed the effect of water vapour and the minor effect of nitrous oxide (Hayes, Westenskow and Jordan, 1983), but this source of error can be avoided by setting the zero on the EMMA while passing through it a mixture of 70% nitrous oxide and 30% oxygen humidified at the appropriate temperature. This method was used for data reported in table III, but the results are less consistent than those obtained with the mass spectrometer.

When the sensor of the EMMA is used in the breathe-through configuration to record inspiratory and expiratory vapour concentrations, the fluctuations in temperature and humidity during inspiration and expiration can be reduced by inserting a heat/moisture exchanger between the patient and the sensor. This was not a problem in our apparatus as only end-tidal gas, saturated with vapour at close to body temperature, entered the cell. The water vapour artefact was, therefore, constant.

The end-tidal sampler would seem to be particularly convenient for use with anaesthetic vapour analysers with a response time which is too slow for the respiratory frequencies which may be encountered in spontaneously breathing patients during anaesthesia. These include refractometers (Hulands and Nunn, 1970) which are not intended for breath-by-breath analysis. In addition, the Datex "Normac" Anaesthetic Agent Monitor does not respond to frequencies in excess of 18 b.p.m. (Luff and White, 1985) and the Engstrom EMMA anaesthetic gas monitor is only suitable for frequencies up to about 12 b.p.m. (Luff and White, 1981). While these instruments are satisfactory during artificial ventilation when the respiration can be maintained at an appropriate frequency, they are unsuitable during spontaneous breathing when frequencies in excess of 30 b.p.m. are commonplace (Nunn, 1964). Modification of a continuous flow analyser to place the sample cell in line with the end-tidal sampler would require calibration under the same conditions of use.

The sampler can also be used for end-tidal measurement of oxygen concentration with the oxygen probe of a slowly responding analyser (such as a fuel cell) in the sampler. However, since several breaths are required to equilibrate the sampler contents with end-tidal gas, it would be too slow to be an effective oxygen warning system.

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D-PENICILLAMINE INDUCED MYASTHENIA GRAVIS

Its Relevance for the Anaesthetist

M. J. FRIED AND D. T. PROTHEROE

SUMMARY

The case of a 57-year-old woman with rheumatoid arthritis is presented to illustrate the rare occurrence of a myasthenic syndrome induced by D-penicillamine, which led to prolonged (5.25-h) postoperative apnoea necessitating artifical ventilation.

Rheumatoid arthritis can be a very mutilating disease and, as a result, the likelihood of patients with rheumatoid arthritis requiring surgery and anaesthesia is increased. D-penicillamine (D-Pen) has been used in the treatment of rheumatoid arthritis and Wilson's disease since the early 1960s. Its true mode of action is unknown, but it appears to modify the immune response. Treatment with D-Pen is associated with many side effects, one of which is the induction of several conditions of which autoantibody production is a feature; for example, systemic lupus erythematosus, pemphigus, Goodpasture's syndrome, polymyositis, autoimmune thyroiditis and myasthenia gravis (Bucknall et al., 1975; Bucknall, 1977; Gordon and Burnside, 1977). A variety of auto-antibodies may be detected following the administration of D-Pen: anti-nuclear factor, anti-striational antibodies and anti-acetylcholine receptor antibodies (Masters et al., 1977; Russel and Lindstrom, 1978; Vincent, Newsom-Davis and Martin, 1978).

It is this last group of antibodies which is of interest to the anaesthetist, as their presence may have a synergistic effect in precipitating prolonged postoperative apnoea when non-depolarizing neuromuscular blocking agents are used as part of the anaesthetic technique (Argor and Mastaglia, 1979).

Finally, it is interesting to note that, although D-penicillamine-induced myasthenia gravis (D-Pen MG) is well known to physicians, a literature survey back to 1960 yielded only one report of postoperative apnoea secondary to D-Pen MG prolonging neuromuscular blockade (Blanloeil et al., 1980).

CASE REPORT

A 57-year-old woman (60 kg) with a 13-year history of seropositive rheumatoid arthritis had been treated with first and second line drugs. In 1982 she underwent, uneventfully, an elbow replacement, which was carried out under general anaesthesia.

In October 1983 D-Pen was commenced in a dose of 125 mg day^{-1}. In July 1984 the patient underwent an ankle arthroplasty when her medication consisted of D-Pen 375 mg day^{-1} and ranitidine 150 mg 12-hourly, the latter used to treat duodenal ulceration which had occurred following indomethacin therapy. Nothing untoward was elicited during her preoperative assessment and her muscle power seemed limited only by the rheumatoid arthritis.

Anaesthetic management

Premedication with papaveretum 10 mg and hyoscine 0.2 mg was administered 1 h before surgery. Thiopentone 250 mg and papaveretum 10 mg were used at induction and alcuronium 20 mg was administered to facilitate intubation of the trachea (Portex 8.5-mm cuffed tracheal tube) and to provide muscle paralysis. Suxamethonium was not used. IPPV was carried out using a Manley ventilator with a tidal volume of 600 ml and a minute volume of nitrous oxide 5 litre and oxygen 2.5 litre. The maintenance of anaesthesia

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M. J. FRIED, B.SC., M.B. B.S.; D. T. PROTHEROE, M.A., F.F.A.R.C.S.; Department of Anaesthesia, Royal United Hospital, Combe Park, Bath, Avon.

Correspondence to M.J.F.

involved further injections of papaveretum 10 mg and droperidol 2.5 mg. Just after induction, cephradine 1 g was given. A 5-mg aliquot of alcuronium was given 2.75 h before antagonism of neuromuscular blockade to ensure absolute relaxation at a particularly delicate stage of the operation. Enflurane 0.6–5% was used for a short period to stabilize the arterial pressure, but this was withdrawn 45 min before antagonism. The anaesthetic was maintained for 3.75 h and antagonism was attempted with atropine 1.5 mg and neostigmine 3.75 mg, in divided doses. However, adequate spontaneous ventilation could not be established despite the administration of doxapram 50 mg and naloxone 0.2 mg. The patient was, therefore, transferred to the I.C.U. for continued IPPV (modified Brompton Manley ventilator) with an oxygen:air mixture (1:5 litre min^{-1}). Blood-gas analysis at this time showed a pH 7.47, $P\text{O}_2$ 11.34 kPa, $P\text{CO}_2$, 4.21 kPa and a base excess +1.5 mmol litre^{-1}. Light sedation and amnesia were maintained with midazolam 7.5 mg but no further analgesia was required. Communication was possible with the patient, who demonstrated an extremely weak grip in response to commands.

The patient did not "fight the ventilator" nor did she make any respiratory effort for 5.25 h. At this time she began to breathe spontaneously via her tracheal tube. One hour later the trachea was extubated, once the patient was able to produce consistent tidal volumes of 300–400 ml at a respiratory rate of 12 to 15 b.p.m. on 40% oxygen. Blood-gas analysis at this time was pH 7.42, $P\text{O}_2$ 9.98 kPa, $P\text{CO}_2$ 4.32 kPa, and a base excess of +1.4 mmol litre^{-1}.

The postoperative period

On the morning of the first day after operation, the patient was found to be alert and well orientated. However, marked ptosis was noted affecting both eyes, particularly the left, which remained closed unless an active effort was made by the patient to open it. She complained of blurred vision and "seeing double". Severe ophthalmoplegia was elicited, especially in upward and downward gaze. No other symptoms or signs of muscle weakness were apparent.

A day later her rheumatologist made a diagnosis of D-Pen-induced myasthenia gravis based on the convincing history of myasthenic symptoms. She had been taking D-Pen for 6 months, and 6 weeks before her operation had noticed that her sight was blurring. Two weeks later she noticed that she was developing double vision and her eyelids were becoming heavier, especially in the evenings. There was no other history of note and she had no relevant family history.

The D-Pen therapy was discontinued 2 days after the surgical procedure; subsequent recovery was rapid and complete.

DISCUSSION

More than 30 drugs in current clinical use, other than those used in anaesthesia, may interfere with neuromuscular transmission and potentiate non-depolarizing neuromuscular blocking drugs. Awareness of the existence of such effects is important to the anaesthetist to prevent unnecessary morbidity, or perhaps mortality, in what is an eminently avoidable situation (Argor and Mastaglia, 1979). With respect to this presentation, cephradine has not been reported as an inducer of myasthenic syndromes.

Despite the problem of a myasthenic syndrome developing following D-Pen therapy being well known to physicians (Bucknall et al., 1975; Bucknall, 1977), there is a paucity of reports of postoperative complications associated with D-Pen in the anaesthetic literature, a retrospective review of which, to 1960, yielded *one* case report of prolonged postoperative apnoea (15 h) as a result of a presumed D-Pen-induced myasthenic syndrome (D-Pen MG) (Blanloeil et al., 1980). This conclusion was arrived at clinically and was supported by the patient's long term recovery after the withdrawal of the D-Pen. In the present case, the patient required 15 h of IPPV.

The reason for this lack of information may be the infrequent incidence of D-Pen-induced myasthenia (1%); the fact that postoperative apnoea is usually attributed to other agents, for example suxamethonium; or that an insufficient number of acetylcholine receptors are blocked to give significant muscle weakness.

D-pen can give rise to a myasthenic syndrome at any time after the initiation of therapy and with a wide spectrum of doses (0.3–1 g day^{-1}) (Bucknall et al., 1975). Its mechanism of action, in the creation of D-Pen MG, is similar to that underlying spontaneous myasthenia gravis, that is, an immune response whereby auto-antibodies directed at the acetylcholine receptor are produced, with a resultant reduction in end-plate potentials and consequent decrease in muscle power (Vincent, Newsom-Davis and Martin, 1978). The diagnosis of D-Pen MG is a clinical one. Ophthalmoplegia and diplopia are the earliest manifestations, but dysphagia and dysphonia may also occur. The diagnosis is further supported by challenge with an anti-cholinesterase, which should precipitate a dramatic improvement in symptoms, and serological investigations should show increased titres of anti-acetylcholine receptor antibodies. EMG evidence in D-Pen MG is surprisingly sparce in the literature (Fawcett et al., 1982).

Ninety per cent of patients with D-Pen MG have anti-acetylcholine receptor antibodies and, within an individual, the antibody titre is closely associated with the disease status. Withdrawal of the drug leads, in the majority of patients, to a clear and sustained clinical improvement, suggesting a causal relationship. Furthermore, this clinical recovery is accompanied by a progressive decrease in the anti-acetylcholine receptor antibody titre (Vincent, Newsom-Davis and Martin, 1978; Argor and Mastaglia, 1979). The time for antibody titres to decrease by 50% in one study ranged from 35 to 60 days (Fawcett et al., 1982).

We could not include serological or nerve stimulator results, since the patient was confined in a small peripheral hospital without such facilities; we were reluctant to inflict further trauma and the diagnosis was readily and confidently confirmed by an experienced rheumatologist who sees several such cases each year.

The conclusion to be drawn from our experience is that anaesthetists ought to be aware of this problem, since the preoperative findings can be camouflaged or non-existent, and the diagnosis may become clear only in response to direct questioning.

Surgical treatment of patients with rheumatoid arthritis and on D-Pen usually involves the limbs and, therefore, in the planning of anaesthetic technique more consideration may be given to the use of local anaesthesia. If general anaesthesia is considered necessary, atracurium would be the neuromuscular blocker of choice. The procedure should certainly be carried out in an institution with facilities for postoperative artificial ventilation.

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MIGRATION OF AN EXTRADURAL CATHETER INTO THE SUBDURAL SPACE

A Case Report

E. ABOULEISH AND M. GOLDSTEIN

SUMMARY

After repeated, successful extradural injections in a parturient, the extradural catheter migrated into the subdural space. The injection of 3% chloroprocaine 10 ml resulted in an extensive block, which extended to the cranial nerves and paralysed the respiratory muscles. The position of the catheter tip was confirmed by fluoroscopy. Subdural injection should always be suspected when tests for subarachnoid injection are negative, but an extensive block occurs gradually within 15–20 min. Respiration and circulation should be supported until the block regresses.

The subdural space is a potential space between the arachnoid mater and the dura mater. It contains a minute quantity of serous fluid which moistens the smooth surfaces of the two membranes. The space ends at the lower border of the second sacral vertebra, where the filum terminale becomes invested closely by the dura mater (Gray, 1985), and extends into the cranial cavity (Mehta and Maher, 1977). Thus a local anaesthetic injected to the subdural space may spread cephalad and block the cranial nerves. Several cases of extensive blockade occurring after an intended extradural injection of local anaesthetic have been attributed to inadvertent subdural injection (Dawkins, 1969; Conklin and van der Wal, 1980; Soni and Holland, 1981; Collier, 1982; Findley and Shandro, 1982; Pearson, 1984), but there are only a few in which the position of the catheter has been confirmed radiologically (Boys and Norman, 1975; Bridle-Smith, Barton and Watt, 1984; Stevens and Stanton-Hicks, 1985), two of them in obstetric patients (Boys and Norman, 1975; Bridle-Smith, Barton and Watt, 1984).

After repeated successful extradural injections, an extradural catheter has been known to migrate into a blood vessel to produce a toxic reaction after the injection of local anaesthetic (Ravindran, Albrecht and McKay, 1979; Zebrowski and Gutsche, 1979), or into the subarachnoid space to cause extensive spinal blockade (Kalas and Hehre, 1972). Although Hatrick and colleagues (1985) described a patient in whom injection of metrizamide showed both subdural and subarachnoid spread of the dye, no report has, to our knowledge, described the migration of an extradural catheter into the subdural space alone, despite the fact that this space has to be traversed before reaching the subarachnoid space. Our case report describes the migration of an extradural catheter into the subdural space after successful repeated extradural injections in an obstetric patient.

CASE REPORT

A 22-year-old, 69-kg, 165-cm tall patient, who had had a Caesarean section 2 years earlier for cephalo–pelvic disproportion, was admitted to the Labour and Delivery Suite at 41 weeks gestation. Labour was induced by artificial rupture of the membranes and an infusion of oxytocin. At 20.20 h (approximately 4.5 h after admission), pethidine 25 mg and promethazine 12.5 mg were administered i.v. for pain relief. At 01.30 h, the cervix was 4 cm dilated, 80% effaced and the fetal head was at the −1 position. Because of the pain

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EZZAT ABOULEISH, M.B., CH.B., M.D.; MARK GOLDSTEIN, M.D.; Department of Anesthesiology, Medical School, The University of Texas, 6431 Fannin, MSMB 5.020, Houston, Texas 77030, U.S.A.

Correspondence to E.A.

associated with uterine contraction, extradural analgesia was instituted.

With the patient in the left lateral position, a midline approach was made at the third lumbar space using an 18-gauge Tuohy needle and the extradural space was identified by the loss of resistance to the injection of air. The needle was not rotated in the extradural space and aspiration was negative for both blood and cerebrospinal fluid. No paraesthesiae were reported. A 20-gauge Teflon catheter with a single terminal orifice was inserted without resistance. Eight millilitre of 0.5% bupivacaine was injected in 2-ml increments over 5 min. Twenty minutes later, pain relief was obtained with blockade extending from T10 to L4 bilaterally. Systemic arterial pressure remained stable at around 120/60 mm Hg, as measured repeatedly (Dinamap). At 04.10 h, 0.5% bupivacaine 8 ml was injected in the same manner with the same effect as the initial dose. Twenty minutes after the injection the arterial pressure was 122/60 mm Hg. At 08.10 h, 0.5% bupivacaine 10 ml was injected and produced a block to T8, with an arterial pressure of 125/63 mm Hg.

At 08.30 h, fetal scalp pH was measured because of decreased beat-to-beat variability, the probability of late decelerations, and the presence of light meconium staining. The pH was 7.32. At 10.30 h, the fetal scalp pH measurement was repeated because of persistent late decelerations and the patient was sent to the Delivery Room for possible operative intervention. At 10.40 h, 2% chloroprocaine 6 ml was injected through the extradural catheter and produced a block to T8 in 10 min. At 10.50 h the scalp capillary blood sample that had been sent earlier was reported to have "clotted" and a Caesarean section was decided upon because of increasing late decelerations. Ten millilitre of 3% chloroprocaine was injected to the extradural space in 5-ml increments in an attempt to intensify the blockade and extend the dermatomal level to T4. This was reached at 11.00 h, when the arterial pressure was 118/55 mm Hg. Oxygen was administered at a flow rate of 5 litre $\min^{-1}$ by a plastic face-mask, and surgery started.

At 11.08 h, a 3180-gm male infant was delivered with Apgar scores of 8 and 9. The fetal blood-gas tensions and acid–base status were normal. At 11.15 h, the patient complained of difficulty in breathing. Examination of the dermatomal level using pin-prick indicated an extensive block which included the trigeminal nerves. Phonation rapidly became weaker, but the arterial pressure decreased from 115/50 mm Hg to 105/50 mm Hg only. At 11.20 h, because of inadequacy of ventilation, rapid sequence induction using thiopentone 250 mg, suxamethonium 100 mg and tracheal intubation was performed. Ventilation (with 60% nitrous oxide in oxygen) was controlled until 12.00 h, when it was assisted as the respiratory muscles started to recover. At 12.15 h, surgery ended. At 12.30 h, respiration was normal and the trachea was extubated. At 12.40 h, the patient complained of incisional pain, and was given morphine sulphate 10 mg i.m.

Next morning, with the patient's consent, the position of the extradural catheter was examined by injecting 190 mg% metrizamide 3.5 ml under fluoroscopic control. The lateral view showed the dye spreading in the anterior subdural space, just posterior to the vertebral bodies (fig. 1). The

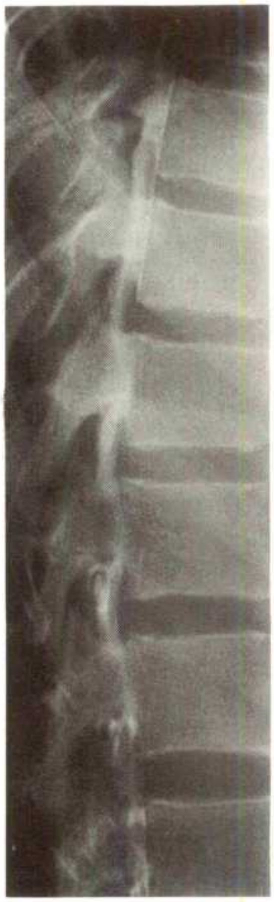

FIG. 1. Lateral view of the vertebral column showing anterior spread of the dye into the subdural space.

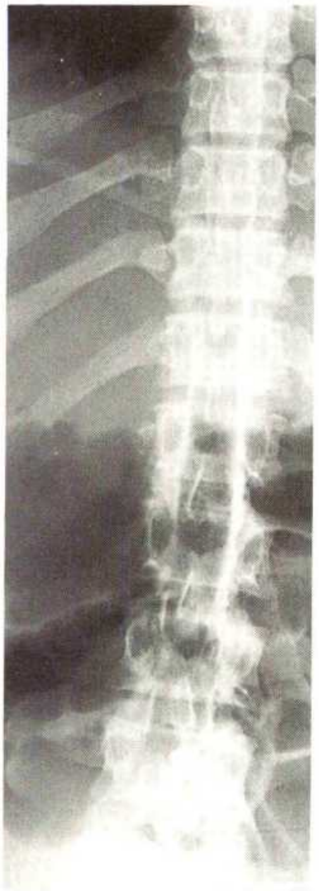

FIG. 2. Anteroposterior view of the vertebral column showing the "rail-road track" appearance and spread of the dye into the subdural space.

anteroposterior view showed the characteristic "rail-road track" appearance with cephalad extension of the dye bilaterally into the upper thoracic region (fig. 2). Fluoroscopy also showed that the dye extended to the upper sacral region and that the tip of the catheter was just behind the body of the 4th lumbar vertebra.

The patient's further stay in hospital was uneventful and she was discharged with her baby on the 5th day postpartum.

DISCUSSION

The differential diagnosis in this case was either migration of the catheter into the subarachnoid space or massive extradural blockade.

The former was excluded in two ways. First, aspiration for cerebrospinal fluid was negative before and after injection, although a negative aspiration test does not always exclude the presence of an extradural catheter in the subarachnoid space. Second, a subarachnoid position of the catheter may be excluded by the time sequence of events. Had the last dose, 3% chloroprocaine 10 ml, been injected to the subarachnoid space, total spinal blockade would have developed within minutes and the patient would have required ventilation for hours. In our patient, the difficulty in breathing occurred 20 min after the injection and lasted for only 40 min. The block regressed so rapidly that the patient required morphine for postoperative pain within 2 h of surgery.

The second possibility was massive extradural blockade. Against this was that the sum of the last two doses, 16 ml of 3% chloroprocaine, could not be considered excessive for a 165-cm woman. Finally, a trigeminal nerve block would not be expected with an extradural block, since the extradural space terminates at the foramen magnum (Mehta and Maher, 1977).

The mechanism for the extensive spread associated with the subdural injection of a solution, whether dye or local anaesthetic, is unknown. We think it is related to the limited capacity of this potential space, which has almost no "escape routes". In contrast, the extradural space is much wider, being about 5 mm posteriorly, and solution may spread out through the intervertebral foramina.

The site of action of a local anaesthetic injected to the subdural space is unknown. In the subarachnoid space, the nerve roots are covered only by the pia mater; in the subdural space they are covered by the pia and arachnoid maters; while in the extradural space they are covered by these two thin layers and the thicker dura. This difference in the sheathing of the nerve roots may explain the clinical picture of subdural injection as being midway between that of an intrathecal and an extradural blockade. It is stated that the subdural space has more potential capacity posteriorly and laterally (Shapiro, 1975). This explains the rarity of motor paralysis and hypotension because of sparing of the anterior nerve roots which transmit the motor and sympathetic nerve fibres (Boys and Norman, 1975). However, in this case, motor paralysis was evident because of the anterior spread of the local anaesthetic, the high concentration, and the large dose. The anterior, rather than posterior, spread of the local anaesthetic is difficult to explain, considering the posterior approach to the subdural space. However, adhesions or difference in the resilience of tissues might have been the cause. With subdural injection, the systemic arterial pressure is usually stable or is accompanied by a gradual and mild degree of hypotension (Boys and Norman, 1975; Machanda et al., 1983; Bridle-Smith, Barton and Watt, 1984; Stevens and Stanton-Hicks, 1985). In our case, hypotension was expected because of the extensive sympathetic blockade associated with spread of solution to the anterior nerve roots. However, despite warm dry hands and bilateral miosis, arterial pressure did not decrease significantly. This might have been the result of the fact that the patient was in labour, cardiac output was increased, the fetal membranes were ruptured (Abouleish, 1977), the main episode occurred after the baby had been delivered, and the patient was adequately hydrated by the administration of 2000 ml of fluid during the 1 h before the final injection.

With extradural anaesthesia, a test dose is recommended to exclude an intravascular or subarachnoid catheter position. Although it would be ideal to test for subdural injection, this cannot be done routinely because of the long latent period, 15–20 min, and the extreme rarity of the condition. With subarachnoid injection, whether for anaesthesia or radiology, the incidence of subdural injection (1–13%) is much greater (Bromage, 1978). The reason is that, each time a subarachnoid injection is attempted, the subdural space has to be traversed, and unintentionally the injectate may be totally or partially placed in the subdural space. On the other hand, with extradural injections the intention is to stay posterior to the dura and the subdural space.

In conclusion, subdural migration of an extradural catheter is possible and should be borne in mind. It should be suspected when an aspiration test for cerebrospinal fluid is negative, a test dose for subarachnoid block is negative, and when a block too extensive to be explained on the basis of an extradural injection occurs 15–20 min after injection. Respiration and circulation should be supported until the block wears off. The position of the catheter can be confirmed by injecting a water-soluble radiopaque dye under fluoroscopic control. This will show a "rail-road track" appearance with subdural injection, compared with the "sausage-like" appearance of subarachnoid injection (as the dye collects in the cul-de-sac of the cauda equina region), and the "tree-like" appearance of extradural injection (as the dye spreads to the paravertebral region along the nerve roots through the intervertebral foramina).

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Br. J. Anaesth. (1986), 58, 1198–1208

CORRESPONDENCE

MATERNAL AWARENESS

Sir,—The recent account of maternal and neonatal responses by Crawford, Lewis and Davies (1985) cannot be allowed to pass unchallenged.

An open study is reported of 777 mothers who were, prospectively and randomly, given various concentrations of trichloroethylene (0.2 or 0.3%) or halothane (0.2, 0.3, 0.4 or 0.5%) in nitrous oxide 4 litre min^{-1} and oxygen 8 litre min^{-1} "to maintain *anaesthesia* (the term coined by Oliver Wendell Holmes for the state of "insensibility") at Caesarean section".

The authors have previously demonstrated (Crawford et al., 1976) that low concentrations of inhalation agents under similar circumstances carry an appreciable incidence (5%) of unpleasant awareness. In this study, the use of 0.2% trichloroethylene (even in 40% nitrous oxide) is difficult to justify (9.6% aware) when trichloroethylene was approved by the Central Midwives' Board, to be used in higher concentrations in air by *awake* patients in labour. Similarly, it appears unwarranted to use very low concentrations of halothane when 0.4% halothane in 33% nitrous oxide can result in awareness (Tunstall, 1980), and 0.5% halothane had been shown 15 years previously to be safe and not to be associated with recall (Moir, 1970). The likelihood of awareness was apparently not even considered until the day following operation, although patients in the lowest concentration groups required considerably greater total doses of suxamethonium—indicative of the possibility of the horrific combination of paralysis with awareness. On the following day the patients were initially merely asked if they had had any dreams during the operation, this despite methods being available for many years to determine, at the time of operation, whether the patient is experiencing wakefulness (Tunstall, 1979).

Other aspects of this study are equally disquieting: no local ethics committee approval was sought; informed consent was not obtained. There is nothing to suggest that these patients were made to understand that many of them stood a considerable chance of awareness.

The authors admit to conducting an open study in which the incidence of awareness plus unpleasant dreams was unacceptably high, but it should not have taken 26 of 264 patients to demonstrate that awareness is unacceptable when concentrations (0.4–0.5%) of halothane sufficient to reduce wakefulness to justifiable levels do not carry undue hazard.

Publication of such a report does credit only to the fortitude of the patients.

C. E. Blogg
J. Edmunds-Seal
Oxford
D. Brighouse
P. I. E. Jones
London
F. P. Buckley
Washington, U.S.A.
D. M. Jackson
Swindon
M. Styles
Northampton

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Sir,—Thank you for the opportunity to reply to this splendidly spirited letter.

As your correspondents will certainly know, during the past several decades a multitude of studies have been undertaken in an attempt to define a technique of general anaesthesia for Caesarean section which will provide for safety and—if possible—comfort for the mother whilst guarding against any observable degree of drug-induced neonatal depression. My own efforts in this field have resulted in at least six successive "refinements" of a basic technique. Examination of the potential value of each refinement has usually been conducted—I believe advisably— in the mode of a comparison with the previously adopted technique. Such was the procedure in the study to which Dr Blogg and his colleagues have taken exception.

I re-iterate that we are interested in the condition of both mother and infant. It is only in very recent years that many obstetric anaesthetists (including myself) have begun to form the opinion that, in certainly the great majority of cases, a slight and probably evanescent degree of neonatal depression caused by the transplacental accretion of a volatile anaesthetic agent is of virtually no consequence to the well-being of that infant, and that thus the elimination, as far as is possible, of maternal discomfort should be the more important objective. Incidentally, it is worth recording that, internationally, many neonatologists do not accept the former contention.

Our objective in this study was thus to determine whether or not, by providing a higher concentration of the volatile agent, we could reduce significantly the previously encountered incidence of "maternal awareness plus unpleasant dreams" (which was, by the way, 2.5% among the total group of mothers given 0.2% trichloroethylene) without promoting an unacceptable increase in the incidence of drug-induced neonatal depression.

In our previous study (Crawford et al., 1976) to which your correspondents refer, we compared the use of 0.1% trichloroethylene (which, before the start of the investigation had, for some time, been our standard choice) with that of the 0.2% concentration. As a result of that investigation the use of 0.2% became our routine. When the study under review was designed, we chose to include, in randomized fashion, the standard technique along with others involving higher concentrations. I believe that choice to have been both ethically acceptable and scientifically appropriate. May I, perhaps, quote from our previous report (Crawford et al., 1976): "As only two (0.6%) of the patients in the combined 0.2% series recollected discomfort during the operation, we are reluctant to advise an increase in the depth of anaesthesia to reduce the incidence of these complications." We have now formally investigated the problem and as a result have assuaged our reluctance.

I think it important that there should be discussion—and, if possible, agreement—on the matter of when a previously established procedure should be included in a randomized trial of a proposed advance upon that procedure. My own opinion is that, in the general context of clinical activity, it is necessary to the validity of the investigation that the procedure to be studied should be compared in randomized fashion with that which is currently in use, unless the results of the latter have been truly disastrous, in which circumstance, of course, it should have been discontinued. Yet there is another philosophy which apparently contends that all options remain open. For example, in a study recently reported by a renowned team of obstetric anaesthetists (Abboud et al., 1985), a comparison of several techniques of general anaesthesia for Caesarean section included one in which the agents administered after induction were limited to equal quantities of nitrous oxide and oxygen, with a resultant incidence of 12% awareness. We used a similar technique 15 year ago (Crawford, 1971) and reported an associated incidence of "awareness plus unpleasant dreams" of 26.3% in a series of elective Caesarean sections.

J. Selwyn Crawford
Birmingham

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ANAESTHESIA FOR SURGERY IN A PATIENT WITH A TRANSPLANTED HEART

Sir,—We were extremely interested in your recent Case Report on Anaesthesia for a Patient with a Transplanted Heart (Bricker and Sugden, 1985). We have had experience in both elective and emergency anaesthesia for the cardiac transplant patient and thought that our recent observations might be of some interest to your readers.

Between January, 1968 and May, 1983, 261 patients underwent cardiac transplantation at Stanford University Hospital. Eighty of these patients subsequently underwent 136 anaesthetics for a variety of surgical procedures, both emergency (55%) and elective (45%). Surgery varied from 2 h to 6 yr after transplant. Only 4.4% of these patients received regional anaesthesia. The remainder had general anaesthesia. However, this should not be taken to mean that regional anaesthesia has no place in non-cardiac surgery in the patient with a transplanted heart. Between February 1976 and October 1984, 19 total joint replacements for steroid-induced osteonecrosis have been performed on heart transplant patients at Stanford Hospital. These included 17 total hip replacements and two total knee replacements. General anaesthesia was utilized in 16 of these procedures and regional anaesthesia, either subarachnoid or extradural blockade, in the remaining six. There were no intraoperative or postoperative problems related to anaesthesia.

It is clear that, with refined cardiac transplantation techniques, improved criteria for patient selection, cyclosporine immunosuppression, and improved anaesthetic and monitoring techniques, cardiac transplant surgery can return over 80% of recipients to their preoperative state. At present there are at least 25 American Medical Centers which are establishing or have established transplant programmes. The same trend can be seen in the United Kingdom. The number of transplant recipients who develop steroid-induced osteonecrosis or other conditions requiring surgery will continue to increase and these patients may eventually come to surgery.

We feel that, provided the basic principles of fluid management, aseptic technique and appropriate monitoring are carried out, these patients present an acceptable risk for regional anaesthesia.

S. I. Samuels
J. Wyner
Stanford, California

REFERENCE

Bricker, S. R. W., and Sugden, J. C. (1985). Anaesthesia for surgery in a patient with a transplanted heart. *Br. J. Anaesth.*, **57**, 634.

Sir,—We read with interest the report by Bricker and Sugden (1985) on anaesthesia for surgery in a patient with a transplanted heart. Anaesthesia for such patients will become a much more common occurrence in the future. The anaesthetic aspects of the Harefield cardiac transplantation programme have been reviewed recently (Grebenik and Robinson, 1985) and a number of patients in this series have required anaesthesia following their transplants.

Cardiac transplantation is now an established and effective treatment for endstage cardiac failure and has a 1-year survival rate of over 80%. More than 200 operations have been performed at Harefield with 158 patients surviving. About 120 operations have taken place at Papworth. With the addition of a third transplant centre and increased funding, numbers will continue to grow. The recent DHSS report on cardiac transplantation envisaged the level of potential demand for transplants in the early 1990s at 800 operations per year. Following surgery, heart transplant recipients are at risk from complications associated with heavy immunosuppressive regimens, for example chronic infections, aseptic necrosis of the hip, the development of neoplasms and, in particular, lymphomas. Patients will usually be treated for these complications at their local hospitals rather than being referred back to the transplant centre. As the number of long-term survivors continues to grow it is to be expected that increasing numbers of anaesthetists will be asked to deal with them.

We would like to add some further points to those made by Drs Bricker and Sugden. Most heart transplant patients will now be on an immunosuppressive drug regimen that includes cyclosporin A. Cyclosporin is a powerful suppressor of cell-mediated immunity, the most important side effects of which are renal impairment—often with fluid retention and hepatotoxicity. A dose-dependent and usually reversible increase in serum creatinine and urea concentrations occurs. Further renal insults may be additive and can rapidly precipitate acute renal failure. The use of systemic antibiotics with nephrotoxic effects may necessitate an adjustment in cyclosporin dosage. The measurement and maintenance of urine output during and after major surgery is of prime importance and close monitoring of serum creatinine, urea, bilirubin and liver enzymes is required.

We would like to emphasize that information regarding the functional status of these patients should be readily available from the transplant hospital, since they are kept under regular review. Routine transvenous endomyocardial biopsies are performed to assess the presence of acute or chronic rejection. Coronary angiography and left ventriculography are used, together with other non-invasive techniques to assess graft function.

C. R. GREBENIK
P. N. ROBINSON
London

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Grebenik, C. R., and Robinson, P. N. (1985). Cardiac transplantation at Harefield. *Anaesthesia*, 40, 131.

Sir,—Drs Bricker and Sugden (1985) considered that spinal or extradural analgesia was contraindicated in their patient with a transplanted heart, partly because of the risk of hypotension. We wish to report a patient in whom subarachnoid analgesia was used uneventfully in such a patient.

A 52-year-old man was scheduled for a transurethral resection of the prostate some 9 months after cardiac transplantation. He weighed 83 kg and was markedly Cushingoid in appearance. His daily medication included prednisolone 10 mg, cyclosporin 200 mg 12-hourly, dipyridamole 100 mg 8-hourly, nifedipine 20 mg 12-hourly and Moduretic (hydrochlorothiazide 25 mg and amiloride hydrochloride 2.5 mg) one tablet. Systemic enquiry revealed dyspnoea on exertion, but he was otherwise well. Haemoglobin concentration and electrolyte concentrations were within normal limits.

Diazepam 10 mg by mouth and hydrocortisone 100 mg i.m. were given about 1 h before anaesthesia. On the patient's arrival in the anaesthetic room, an i.v. infusion of lactated Ringer's solution was started. With the patient in the sitting position, a 22-gauge spinal needle was inserted at the second lumbar space and plain bupivacaine 3.5 ml was injected over 10 s. The patient was then placed in the supine lithotomy position with a 10° head-down tilt.

Analgesia to pinprick developed bilaterally to the level of the 9th thoracic dermatome 10 min after injection and did not spread further. Surgery commenced and lasted 25 min. His arterial pressure decreased from 140/100 to 130/90 mm Hg at 40 min. Throughout surgery the heart rate remained unchanged at 78–82 beat min^{-1} and no ECG changes were noted. Blood loss was estimated to be minimal for a 10-g resection. Recovery, from the block and the operation, were entirely uneventful and the patient was discharged from hospital 5 days later. To date he remains well.

Hypotension during spinal anaesthesia is almost always associated with a block to the upper thoracic dermatomes, and is probably as much the result of an imbalance between the activity in parasympathetic and sympathetic nerves, as of an absolute decrease in the latter. In the denervated, transplanted heart, rate is dependent on humoral factors and cardiac output is controlled by venous return and myocardial contractility. The judicious use of posture and i.v. fluids, during spinal anaesthesia, will maintain venous return, and avoids the need for anaesthetic agents known to depress myocardial function. Furthermore, spinal anaesthesia offers the advantage of supressing the humoral response during surgery and the adverse effects of increased circulating catecholamines upon the myocardium may be avoided.

This case report demonstrates that a carefully administered spinal anaesthetic may be considered to be an acceptable technique in a patient with a transplanted heart. Theoretically, it may offer some advantages.

D. W. MCKEOWN
I. R. ARMSTRONG
Edinburgh

REFERENCE

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ANAESTHESIA FOR DAY-STAY LAPAROSCOPY

Sir,—Laparoscopy, particularly for female sterilization and dye investigation of tubal patency, is a short procedure frequently performed on a day-case basis. An anaesthetic technique which avoids the necessity for the rapid and complete antagonism of a non-depolarizing neuromuscular blocker may be advantageous.

Laparoscopy requires the Trendelenberg position and abdominal insufflation, usually with carbon dioxide. These conditions predispose to an increase in arterial carbon dioxide tension (Pa_{CO_2}) during spontaneous ventilation (Seed, Shakespeare and Muldoon, 1970) and, if halothane is used as the inhalation agent, there is an increased risk of cardiac arrhythmia (Desmond and Gordon, 1970). However, Harris, Plantevin and Crowther (1984) concluded that there was no contraindication to patients breathing spontaneously with enflurane during laparoscopy, provided that the intra-abdominal pressure did not exceed 25 mm Hg. Isoflurane also has a low incidence of cardiac arrhythmia and causes less respiratory depression than enflurane (Eger, 1981). Therefore, it was decided to compare isoflurane with enflurane in patients breathing spontaneously during laparoscopy.

Forty patients (ASA 1 or 2) presenting for elective laparoscopy were randomly allocated to one of two groups receiving either enflurane or isoflurane. Premedication was with papaveretum and hyoscine. The trachea was intubated and the patients allowed to breathe spontaneously. Arterial pressure, heart rate, tidal volume, respiratory rate and end-tidal carbon dioxide tension were monitored. The electrocardiogram was recorded continuously on to magnetic tape from before induction until the patient left the recovery area. Student's *t* test was used to compare variances and mean values and the Chi-squared test to compare the frequency of arrhythmias between the two groups.

There were no significant differences between the two groups with regard to age, weight, duration of anaesthesia, arterial pressure or heart rate. The values for $P_{\text{E}_{\text{CO}_2}}$, minute volume and respiratory rate are shown in table I. There were no significant differences between the means of these values for the two groups. The maximum increase in $P_{\text{E}_{\text{CO}_2}}$ when comparing the values at the end of insufflation with those at the start of the operation in any patient was 1.33 kPa. Eighteen patients showed a decrease in $P_{\text{E}_{\text{CO}_2}}$ during insufflation.

TABLE I. *End tidal carbon dioxide tension, minute volume and respiratory rates immediately before insufflation compared with those immediately after removal of the laparoscope*

	$P_{\text{E}_{\text{CO}_2}}$ (kPa)	Minute volume (litre min^{-1})	Respiratory rate (b.p.m.)
Group E			
Before insufflation			
Mean (SEM)	6.6 (0.15)	3.94 (0.34)	16 (0.69)
Range	5.6–7.8	2.1–8.1	10–23
End of insufflation			
Mean (SEM)	6.6 (0.15)	4.61 (0.37)	19 (1.22)
Range	5.3–7.7	2.2–8.8	11–35
Group I			
Before insufflation			
Mean (SEM)	6.2 (0.18)	3.87 (0.29)	18 (1.22)
Range	4.8–8.0	2.2–6.3	9–26
End of insufflation			
Mean (SEM)	6.2 (0.19)	5.12 (0.37)	20 (1.40)
Range	4.3–8.1	2.8–9.9	12–34

Six patients developed an arrhythmia (either unifocal ectopic or bigemini) during the course of the study. Three occurred before induction and one patient developed bigemini during intubation. All four of these patients reverted to sinus rhythm before insufflation. Arrhythmia during insufflation occurred in none of the patients receiving enflurane and in two of the patients receiving isoflurane. This difference was not significant. No arrhythmia occurred in any patient after the carbon dioxide had been removed from the abdomen.

Laparoscopy for routine procedures may be very short in duration, for example as short as 13 min in our study. Even with the newer non-depolarizing blockers atracurium and vecuronium, rapid and complete antagonism after such a period may be difficult. Careful monitoring of neuromuscular function is important because simple clinical evaluations of residual blockade may be misleading (Jones, 1985). In studies of postoperative morbidity following outpatient anaesthesia involving neuromuscular blockade there were instances of double vision which may have been caused by residual blockade (Collins, 1984). Therefore an anaesthetic technique which avoids the use of non-depolarizing agents may be advantageous. Also, some surgeons prefer the degree of muscle tone provided by a non-paralysed patient when inserting the laparoscope.

The authors believe that an anaesthetic technique of spontaneous ventilation with enflurane or isoflurane is satisfactory for routine laparoscopy provided that the intra-abdominal pressure does not exceed 25 mm Hg.

J. K. MYATT
M. SMITH
O. M. PLANTEVIN
A. CROWTHER
London

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OXYGEN LOSS FROM ROTAMETER

Sir,—I would like to report a dangerous fault which recently occurred in a Boyle-type anaesthetic machine, which led to a selective oxygen loss from the inspired gas mixture.

Shortly after a patient had been connected via a Bain circuit to a Penlon Nuffield ventilator, cyanosis was noted. A rapid assessment of the position of the tracheal tube, ventilation of the lungs and the anaesthetic machine (the rotameters showing an oxygen flow of 2 litre min^{-1} and a nitrous oxide flow of 4 (litre min^{-1}) revealed no fault. However, an oxygen analyser showed a concentration of only 12%. A replacement machine was installed and the patient's condition improved immediately. The operation continued uneventfully and the patient showed no ill-effects following the procedure.

Subsequent examination of the faulty machine showed an axial tear in the upper rubber grommet of the oxygen rotameter. Despite the machine having been tested (a "single hose" test) before the case, this defect had not been apparent, nor had it been prevented by servicing carried out during the previous week. Clinical observation, confirmed by an oxygen analyser, averted a serious outcome. A pressure leak test, as described by Page (1977) might have brought the fault to light had it been utilized.

Similar occurrences have been reported in this Journal by Bishop, Lerick and Hodgson (1967), Gupta and Varshneya (1975), and from this hospital by Powell (1981). In subsequent correspondence, Rendell-Baker (1981) recommended that the oxygen flowmeter be relocated to the right-hand side next to the flowmeter manifold outlet. This could be done *in situ* at little expense, and with the re-education of users.

May we suggest that manufacturers should consider this design fault, and also alter the replacement schedule for flowmeter grommets? In the meantime, all anaesthetists should be aware of this potential problem. Moreover, this incident illustrates the value of an oxygen analyser in supplementing clinical observation.

M. Dudley
E. Walsh
Bristol

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TREATMENT OF NAUSEA WITH EXTRADURAL DROPERIDOL

Sir,—Following the report on the use of extradural droperidol (Bach et al., 1985) I would like to present some further clinical observations following its use in two patients.

A 57-year-old man presented with bilateral thoracic metastases, mild ascites and pain in the rib cage. Previously, a biopsy of a Virchow's node showed adenocarcinoma, primary site unknown. A thoracic extradural catheter was placed at T10/11 and a twice daily dose of morphine, 12 and 8 mg, produced adequate analgesia. One week later the patient developed nausea and hiccups that were unresponsive to chlorpromazine by mouth. Droperidol was given, mixed together with the morphine, in a twice daily dose of 1.25 and 2.5 mg. Within 1 h of the first dose of droperidol the nausea disappeared, and the hiccups ceased gradually over the next 24 h. The patient remained mobile and could eat normally without signs of sedation or hypotension. The dose of droperidol remained unchanged, although the morphine requirements increased in the terminal stage of his disease, without the return of symptoms. He died 8 weeks after the start of the treatment with morphine–droperidol.

The second patient, a 67-year-old man, presented with left-sided intractable thoraco-abdominal pain, corresponding to the T6–11 dermatome. Two years previously he underwent a left nephrectomy for adenocarcinoma of the kidney. He had been treated for 1 month before admission with chlorpromazine and ketobemidone by mouth, with decreasing effect. Computed tomography showed enlargement of the pre-aortic lymph glands and a mass invading the retroperitoneal space. A thoracic extradural cannula was inserted at L1/2 and morphine was given until a dose of 30 mg, 8-hourly, produced adequate analgesia. The patient remained mobile, but the nausea was unrelieved. Extradural droperidol was started at a dose of 1.25 mg in the morning and 2.5 mg at evening. Following the droperidol the nausea abated, but the effect was short-lived. During the following 2 days the droperidol was increased until doses of 5 mg, 5 mg and 2.5 mg, at 8-hourly intervals, relieved the nausea. The patient continued in full activity and showed no signs of cerebral sedation, or hypotension. The patient died 7 weeks later and, in spite of increasing morphine requirements, the nausea did not return.

The aetiology of the nausea is, of course, speculative and several possibilities exist. Potentiation of the analgesia, although apparently adequate at the time, may have resulted in the disappearance of the symptoms. The nausea may have been a side effect of the extradural morphine *per se*. A further possibility is that the nausea and, in the first patient, hiccups were a result of tumour spread within the abdominal cavity.

Droperidol is a neuroleptic drug with a predilection for certain areas of the brain known to be rich in dopaminergic synapses. It is thought to exert its antiemetic effect by affecting the emetic trigger zone. The absence of behavioural effects and the lack of alpha-adrenergic blockade suggest an antiemetic site of action at the spinal level, possibly by interfering with transmission of noxious impulses in the spinal cord.

M. P. Corbey
Kongsberg

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BLOOD VISCOSITY

Sir,—The study of blood viscosity and its modification is of interest in anaesthesia (Gordon and Ravin, 1978).

Viscosity is a physical property of fluids; blood has a "non-Newtonian" behaviour (its viscosity is not constant, changing inversely with the rate of flow), while plasma has "Newtonian" behaviour (constant viscosity). Factors having some influence on blood viscosity are: haematocrit, plasma proteins (basically, fibrinogen and globulins). The influence of platelets and leucocytes is less important—at an intercellular level the aggregation and deformability of red cells are the most important factors (Goslinga, 1984).

The measurement of whole blood viscosity does not present a defined value at some particular shear rate, but a representation of the behaviour of blood at several degrees of shear rate.

Gramstad and Stovner (1979) studied the effects of anaesthetics containing Cremophor EL on plasma viscosity. Orr and colleagues (1982) reported the effects of Althesin on plasma and blood viscosity after i.v. administration; they found small decreases in plasma and blood viscosity as well as in haematocrit, but these were statistically significant effects only at very low shear rates ($0.945\ \mathrm{s}^{-1}$). More recently, Gibbs, Oh and Chester (1984) found important increases in plasma viscosity after several days of continuous infusion of Althesin.

We have recently studied the effects of propanidid–Cremophor EL on whole-blood viscosity, haematocrit, leucocytes and platelets, after induction of anaesthesia in eight patients, all submitted to short procedures. Propanidid–Cremophor i.v. reduced whole-blood viscosity after 5 min *in vivo* from 0.63 ± 0.3 cP (centipoise) ($P < 0.001$) at $230\ \mathrm{s}^{-1}$ (shear rate). It decreased to 0.8 ± 0.5 cP at $115\ \mathrm{s}^{-1}$ ($P < 0.01$); to 1.9 ± 1.0 cP ($P < 0.01$) at $46\ \mathrm{s}^{-1}$; to 1.7 ± 0.8 cP at $23\ \mathrm{s}^{-1}$ ($P < 0.001$) and to 2.1 ± 0.7 cP at $11.5\ \mathrm{s}^{-1}$ ($P < 0.001$). Haematocrit decreased by 2.3% (ns), haemoglobin by $0.5\ \mathrm{g\ dl}^{-1}$ (ns) and platelets by $23000 \pm 12000\ \mathrm{dl}^{-1}$ ($P < 0.01$).

We believe that there is a different effect of anaesthetics containing Cremophor-EL on blood viscosity, when they are administered for induction (i.e. for short periods and in low dose) when compared with continuous and long-term infusion.

We conclude that, in anaesthetic practice whole-blood viscosity studied *in vivo* and its related haematological factors are of more interest than those factors which depend on plasma viscosity *per se*.

J. GONZALEZ DE ZARATE
J. OJEDA
R. SANZ
Madrid

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CONTINUOUS EXTRADURAL INFUSION OF 0.0625% OR 0.125% BUPIVACAINE

Sir,—I am totally at a loss to identify what lessons Dr Li and colleagues (Li, Rees and Rosen, 1985) intended readers to draw from their report. If the objective of using a continuous infusion of either 0.0625% bupivacaine or 0.125% bupivacaine, at one of the specified rates, was to eliminate or markedly to reduce the hazard specifically associated with bolus top-ups, then manifestly their effort was unsuccessful. Only two of the 20 mothers receiving the more dilute solution did not require a bolus top-up (0.25% bupivacaine 10 ml) and six needed at least three intermittent doses. Among those in receipt of 0.125% bupivacaine, the respective numbers not requiring a bolus top-up were 1, 4, 6 and 7 (grouped according to the rate of infusion), and the numbers needing at least three top-ups were 6, 1 and zero.

Lin and colleagues have convincingly demonstrated that the technique of continuous infusion, as used by them, as a sole form of therapy (superimposed upon a loading dose), provided a very unsatisfactory standard of analgesia in labour. Indeed, it would appear that mothers would be likely to be equally as well satisfied by the receipt of systemic or inhalation analgesia.

No reference is made to the effect of continuous infusion, in contrast to that of intermittent topping-up, upon bladder sensation throughout labour. Was there a relative increase in the incidence of required bladder catheterization among those mothers who did not need supplementary top-ups?

Finally, the authors advocate midwifery assessment of the upper level of sensory block (and presumably of lower limb weakness). I doubt that that would become an accepted item of clinical care in a busy Delivery Suite.

J. SELWYN CRAWFORD
Birmingham

REFERENCE

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Sir,—Dr Crawford also participated in the O.A.A. meeting, 1984, at which this study was presented. So we must not have been as clear as we would have wished then, too.

The introduction states: "The present study was designed to determine the optimum volume of infusion necessary to prolong effectively the interval between top-ups". That volume was 10 ml of 0.125% bupivacaine per hour. That dose (12.5 mg h^{-1}) increased the median interval between top-ups from 145 min in the control mothers to 245 min. Only 31% of these mothers required more than one top-up, compared with 68% of controls for these long (11-h+) labours. Whether this is a useful extension depends upon who is getting up to do the top-up!

It should be safer to use low-dose infusion. If it wears off, then there is very good evidence that the catheter is not intrathecal, so a further top-up should be safe. However, there remains a risk, even from low-dose infusion, of central spread from intrathecal spread. We suggested, therefore, that the midwife should test the upper levels of sensory blockade. We do not believe that estimates of motor weakness are of value since the test is too subjective and, even with a weak concentration of bupivacaine, some mothers still have motor weakness. At present we are testing the midwife's ability to determine upper sensory levels and will present our results in due course.

G. A. D. REES
M. ROSEN
Cardiff

MIDAZOLAM, DIAZEPAM AND PLACEBO AS PREMEDICATION FOR REGIONAL ANAESTHESIA

Sir,—Understanding of the above study by Reinhart and others (1985)) would be enhanced if the authors clarified the points listed below:

(1) What is the concept of anxiety underlying the chosen psychometric procedure? Implicit in the efficacy score is an emphasis, not on anxiety, but on sedation, in that there are only three judgements of apprehension, but seven on sedation/excitement. The latter dimension is only a part of such a complex emotion as anxiety, and is far from being identical with it.

The only subjective rating also deals with the quality of sedation. At what time was this measurement taken? In a retrospective judgement, subjective ratings could have been influenced by the amnesic effects of midazolam. Sedation is not evidence of an anxiolytic effect. As there were no other assessments of emotions, maybe a drowsy patient felt helpless, a very common feeling before an operation.

(2) What kind of information did the anaesthetist use in order to rate apprehension and excitement? The report lacks a description of behavioural categories for rating anxiety and excitement, which are most important in observer ratings. Further, because there was no independent second rater, the reliability of the ratings is questionable. The anaesthesist also registered the physiological reactions—arterial pressure and heart rate. It is not clear to what degree these observations of

the physiological variables could have determined the psychological ratings.

(3) The groups were not compared with regard to psychometric indices. Thus it cannot be excluded that one group differed from the other in actual levels of preoperative anxiety and in coping abilities.

I feel that this study does not help to clarify the preoperative needs of the patient to prepare himself for such a stressful event in an adequate way.

S. Höfling
Munchen

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Sir,—To evaluate two different benzodiazepines as premedicants for regional anaesthesia, we chose a method introduced for this purpose by Dundee, Moore and Nicholl in 1962. This method was used to study drugs given before anaesthesia for their sedative and anxiolytic properties as well as for undesirable side effects. The same authors re-evaluated their method after more than 10000 observations and confirmed its usefulness under standardized conditions—number of visits paid to the patient, nature and duration of operation, surroundings, etc.—for collection of information concerning the subjective effects of different preoperative medications (Morrison, Hill and Dundee, 1968). Our study was not undertaken to clarify *all* the "preoperative needs of the patients", but only to study the effects of midazolam compared with diazepam and placebo. The study design adequately fulfilled the postulated criteria for comparable conditions for all three groups and, therefore, in our opinion the observed differences in efficacy between the drugs are real and reproducible.

To some questions in detail. The quality of sedation was not the only subjective rating, but all patients not asleep were also asked whether the felt anxious or not. The patients asleep were judged not to be anxious. It cannot be ruled out that the amnesic effects of midazolam may have influenced the subjective ratings, but no patient complained about the amnesic actions of this drug; on the contrary, patients are usually happy to have no recollection of the anaesthetic and operative procedures. The judgement of excitement was based only on the anaesthetist's subjective view and experience during the study; haemodynamic variables were not taken into account for this purpose. It is true that we did not study psychometric indices before premedication, but we doubt that our randomization—which was successful with respect to distribution of age, sex and type of urological intervention—led to group differences with respect to "anxiety and coping abilities".

K. Reinhart
G. Dallinger-Stiller
R. Dennhardt
G. Heinemeyer
Berlin

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HEWLETT–PACKARD HP47210A CAPNOMETER

Sir,—I was interested to read the article by Dr Kinsella (1985) assessing the Hewlett-Packard HP47210A capnometer. I appreciate that the accuracy of the equipment was being assessed, but I feel that, with the more widespread use of the capnometer, your readers' attention should be drawn to a disconnection hazard associated with this device.

With only moderate pressure by an assistant leaning on the chest, the connections (Airway Adaptor Tubing Couplers No 14373 A/B) joining the adaptor to the ventilator tubing and to the catheter mount are easily dislodged. This problem has been experienced by all the anaesthetists working at The National Hospital for Nervous Diseases on several occasions.

The couplers are recommended for single patient use only, but as with much so called "disposable" equipment, it is not economical to use them once only. Even with a new coupler, repeated lateral pressure will soon dislodge the connections. This is not surprising, as their construction does not conform to British Standard BS 3849, in either dimension or deformability. A newer modification is, in fact, more rigid, but still does not conform to standards, in particular the depth of joint surface. Obviously, if the alarm is "on" one will be warned of a disconnection, but this is not always the case, and besides, is not sufficient excuse for poor design.

It is well recognized that disconnections of anaesthetic circuits can cause morbidity and mortality. I feel that an improved modification would reduce this risk.

R. J. Lenoir
London

REFERENCE

Kinsella, S. M. (1985). Assessment of the Hewlett–Packard HP47210A capnometer. *Br. J. Anaesth.*, 57, 919.

PREMEDICATION AND BODY TEMPERATURE

Sir,—We have observed that adult patients scheduled for surgery arrive in the Anaesthetic Room with a body temperature lower than normal. This might be the result of fasting, the light covering provided during transport, or premedication.

Drugs currently used for premedication such as opiates and phenothiazines might affect central thermoregulation and cause peripheral vasodilatation. This can result in a decrease in body temperature as previously shown in animal studies (Lotti, Lomax and George, 1965). An increase in body temperature was observed after large doses of atropine and hyoscine (Scopolamine) (Eger, 1962).

We decided to investigate the effect of two widely-used

TABLE I. *Results (mean values ± SD)*

	Papaveretum + hyoscine ($n = 40$)	Pethidine + promethazine ($n = 40$)
Aural canal temp. (°C)		
Before	36.7 ± 0.6	36.8 ± 0.4
60 min	36.7 ± 0.5	36.7 ± 0.6
Mean skin temp. (°C)		
Before	32.6 ± 1.0	32.8 ± 1.2
60 min	33.0 ± 0.9	33.4 ± 0.8
Mean body temp. (°C)		
Before	35.3 ± 0.5	35.4 ± 0.7
60 min	35.4 ± 0.6	35.5 ± 0.4

premedications on the redistribution of body temperature in adult patients. We studied 80 patients, ASA I, aged from 15 to 55 yr, who were to undergo elective orthopaedic surgery. The study was conducted in the surgical wards of our hospital during the period June to August. Patients were randomly allocated to two groups, A and B, of 40 patients each. Group A received an i.m. injection of papaveretum 0.3 mg kg^{-1} and hyoscine 0.006 mg kg^{-1}; group B received pethidine 1 mg kg^{-1} and promethazine 0.3 mg kg^{-1}. All patients were covered with one standard sheet and one blanket.

Skin surface (upper chest, arm, thigh and calf) and core (aural canal) body temperatures were measured in the ward before, and 60 min after, the administration of the premedications.

Ambient temperature, relative humidity and air speed of the surgical wards were measured.

The two groups were comparable for age, body weight and height. Aural canal temperature (core) did not change 60 min after premedication in either group. Mean skin temperature increased in both groups by 0.4 and 0.6 °C (ns), respectively. Nevertheless, this increase did not influence mean body temperature (core and surface) in either group (table I).

In conclusion, we were unable to demonstrate a decrease in body temperature 60 min after the administration of either form of premedication.

Z. ANWAR
F. CARLI
Stanmore

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PARANASAL SINUSITIS: A COMPLICATION OF NASOTRACHEAL INTUBATION

Sir,—We were interested to read the case reports (Willatts and Cochrane, 1985) of two patients who developed severe paranasal sinusitis in association with prolonged nasotracheal intubation. We have previously noticed redness and swelling of the skin over the maxillary sinus in some of our patients following nasal intubation. These patients had exhibited signs of infection, although the site was not obvious. Although we did not see a picture quite like that described by the authors, we did obtain x-rays to see if there were changes in the sinuses. These were suggestive of sinusitis. We wondered how common this might be.

Therefore, we decided to undertake a study in 50 patients after approval from the local ethics committee. We elected to take x-rays immediately after either oral or nasal intubation, and on the 4th and 10th days after intubation. The patient was to act as his own control by comparing the sound side with the intubated side. X-rays were obtained in 10 patients, but the study was terminated for technical reasons—the difficulty of obtaining reproducible films with portable equipment. We did, however, see signs suggestive of sinusitis in some "nasal" films, but we did not have sufficient numbers for statistical analysis.

We agree with Willatts and Cochrane (1985) and other authors (Caplan and Hoyt, 1981; O'Reilly et al., 1984), that sinusitis is a recognized complication of prolonged nasotracheal intubation and should be considered when the usual causes of "pyrexia of unknown origin" in the ITU have been eliminated.

C. M. KUMAR
P. G. P. LAWLER
Middlesbrough

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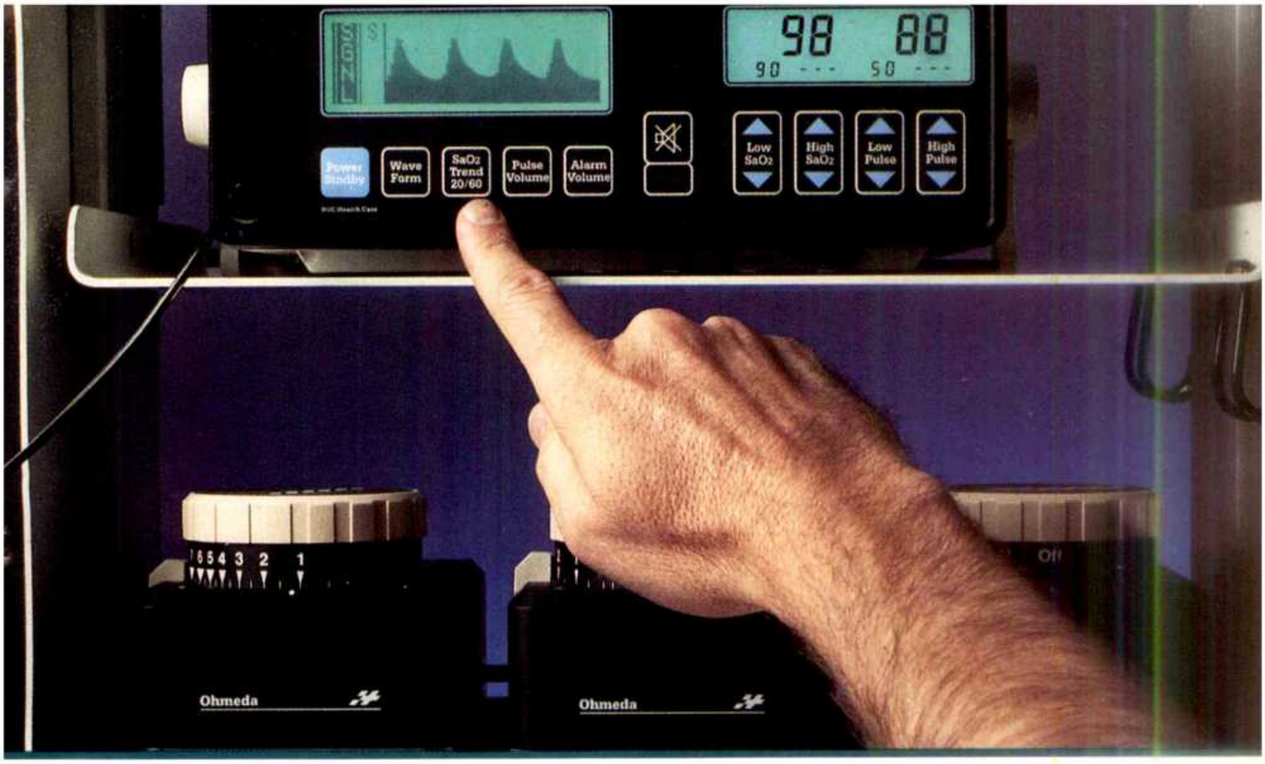

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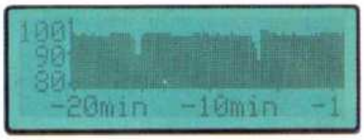

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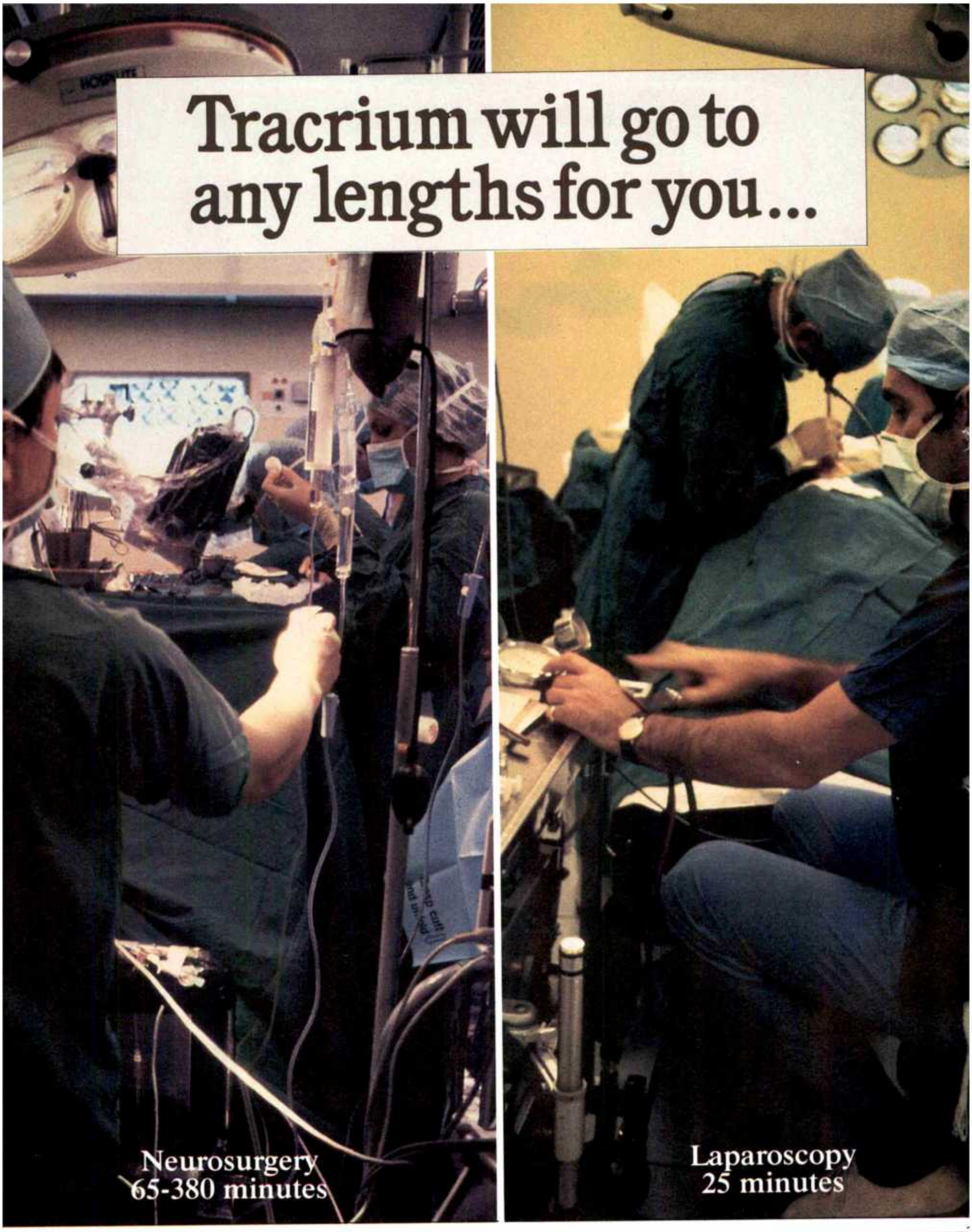

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Contra-indications, warnings, etc. Contra-indicated in patients hypersensitive to atracurium besylate. Tracrium should be used with caution in patients receiving aminoglycosides or polypeptide antibiotics and in patients with myasthenia gravis. In common with all other neuromuscular blocking agents, adequate facilities must be available for endotracheal intubation and artificial ventilation. The neuromuscular block produced by Tracrium may be increased by the concomitant use of inhalational anaesthetics such as halothane. Tracrium should not be mixed in the same syringe with any other agent; in particular it must not be mixed with thiopentone or any alkaline agent, as the high pH would cause inactivation of the Tracrium. As with all other neuromuscular blocking agents the possibility of transient hypotension due to histamine release cannot be excluded. Although animal studies have indicated that Tracrium has no adverse effects on foetal development, nevertheless, like all neuromuscular blocking agents, it should be used with caution in pregnant women. Tracrium may be used to maintain neuromuscular relaxation in Caesarean section as atracurium does not cross the placenta in clinically significant amounts.

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Pulse Oximetry

Editors: **J.P. Payne**, London, **J.W. Severinghaus**, San Francisco

1986. 56 figures. XXII, 198 pages.
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This book contains the proceedings of a three-day symposium organised to introduce the pulse oximeter, an instrument designed to allow the continuous non-invasive monitoring of oxygen saturation levels in a wide range of clinical conditions. The history of blood-gas analysis is outlined in the text together with an account of the physical and physiological principles on which oximetry is based.

Although oximetry is not new, its application has not been widely accepted because the apparatus was both cumbersome and difficult to use. These early difficulties have now been overcome by the development of light emitting diode light sources and the advent of microprocessors which have allowed engineers to incorporate these advances in the evolution of a new generation of relatively inexpensive instruments for non-invasive monitoring. In the case of the pulse oximeter, use has also been made of the pulse added absorbance signal to discriminate arterial oxygen saturation values from capillary and venous values.

Individual chapters highlight the progress that has already been achieved over a wide range of activities from emergency surgery in the neonate to the domiciliary care of the respiratory cripple with particular emphasis on the versatility of the method, its range of accuracy and its limitations. The discussion sections indicate the areas of disagreement of the differences between the measurement of oxygen saturation, tension and content, and an attempt is made to put the contentious aspects into perspective.

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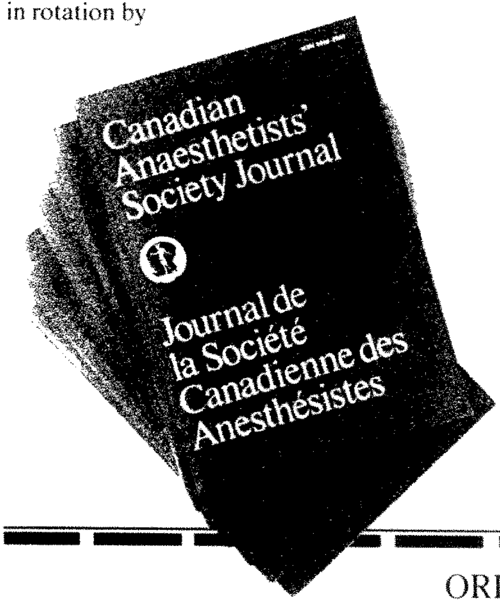
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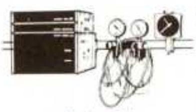
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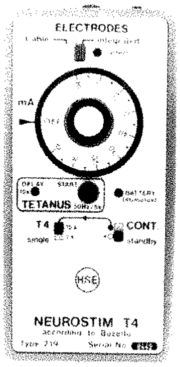

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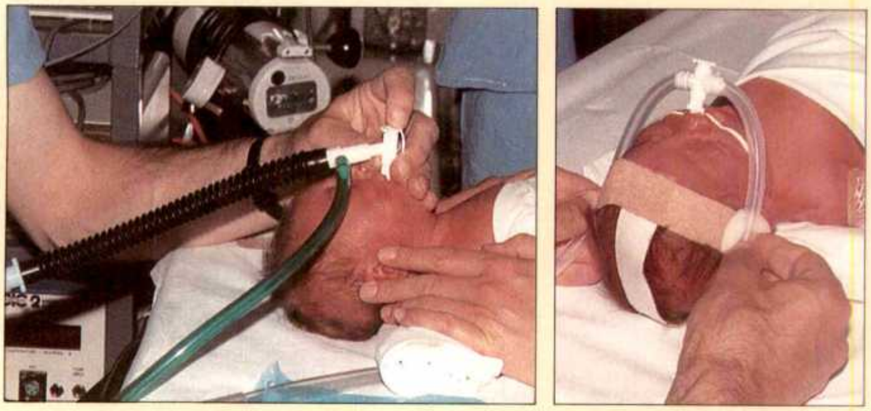

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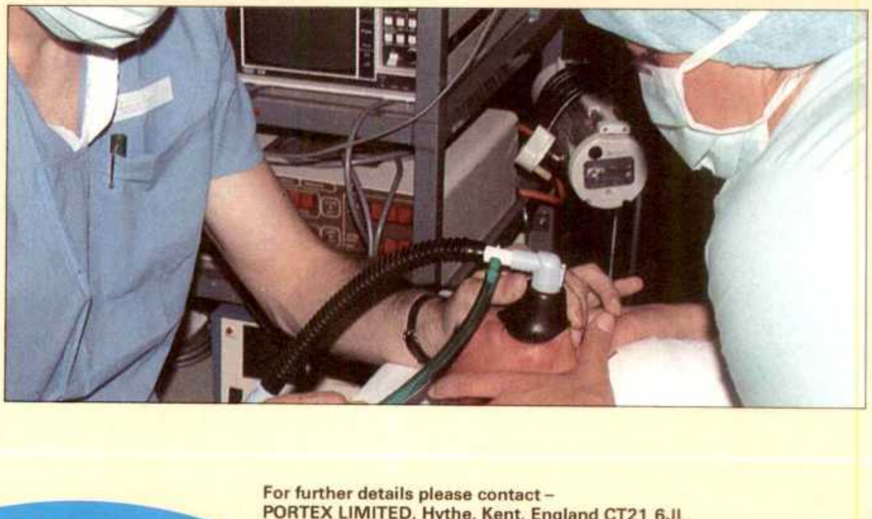

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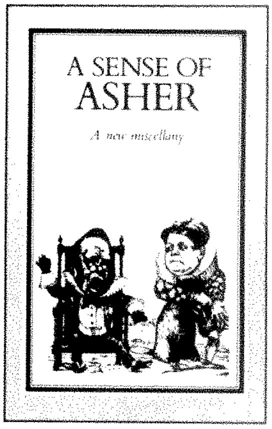

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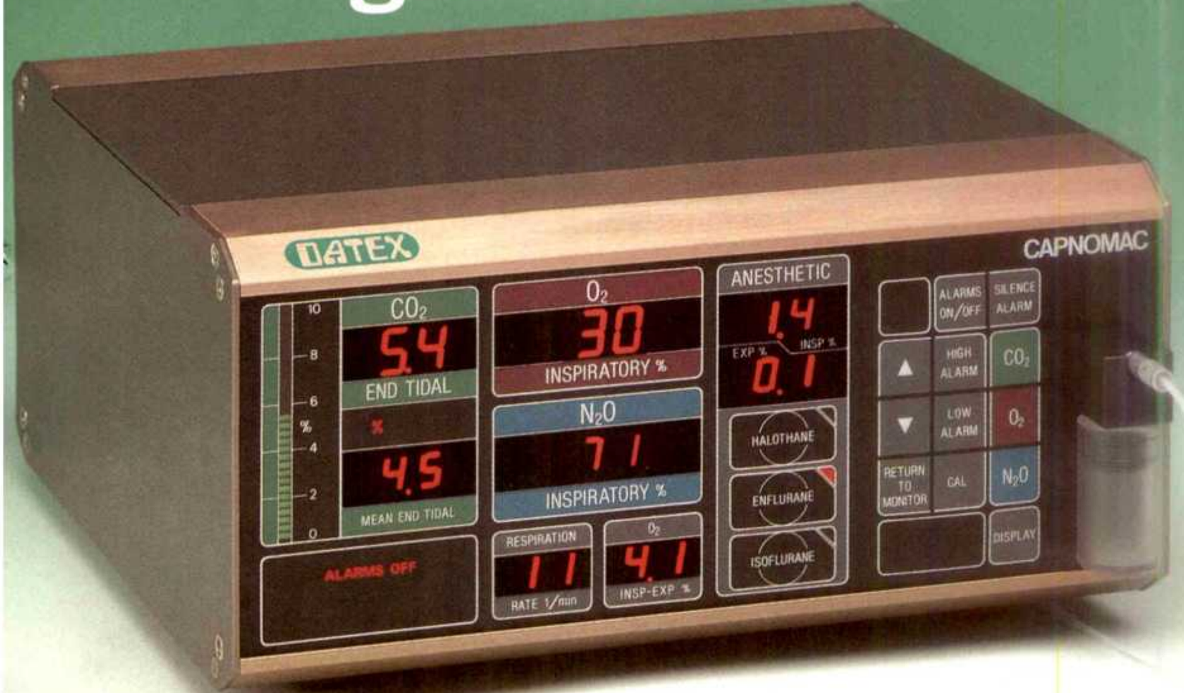

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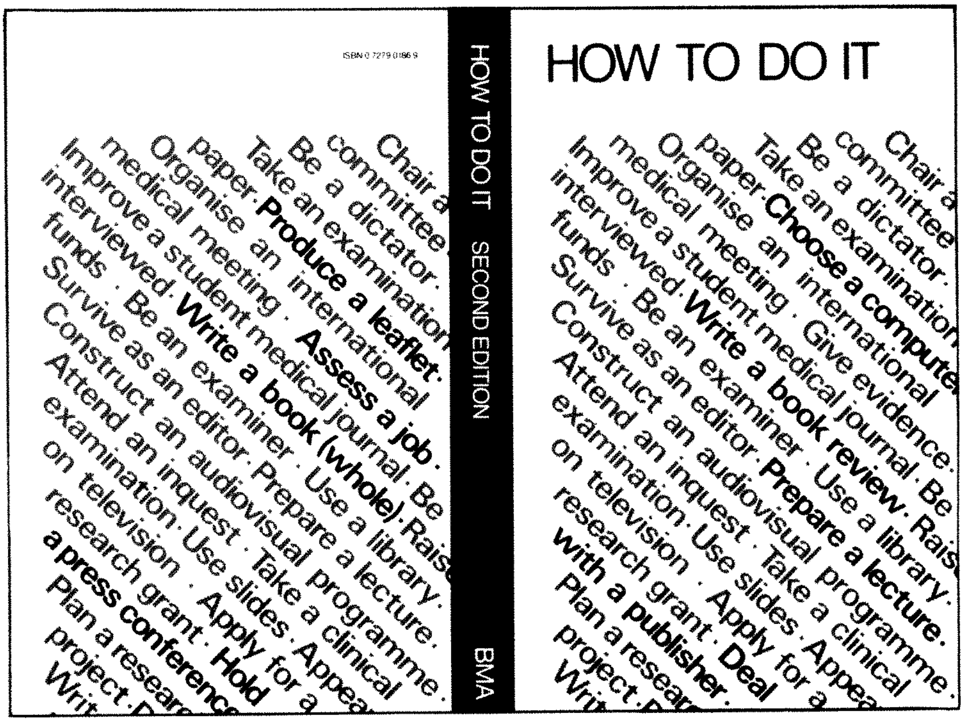
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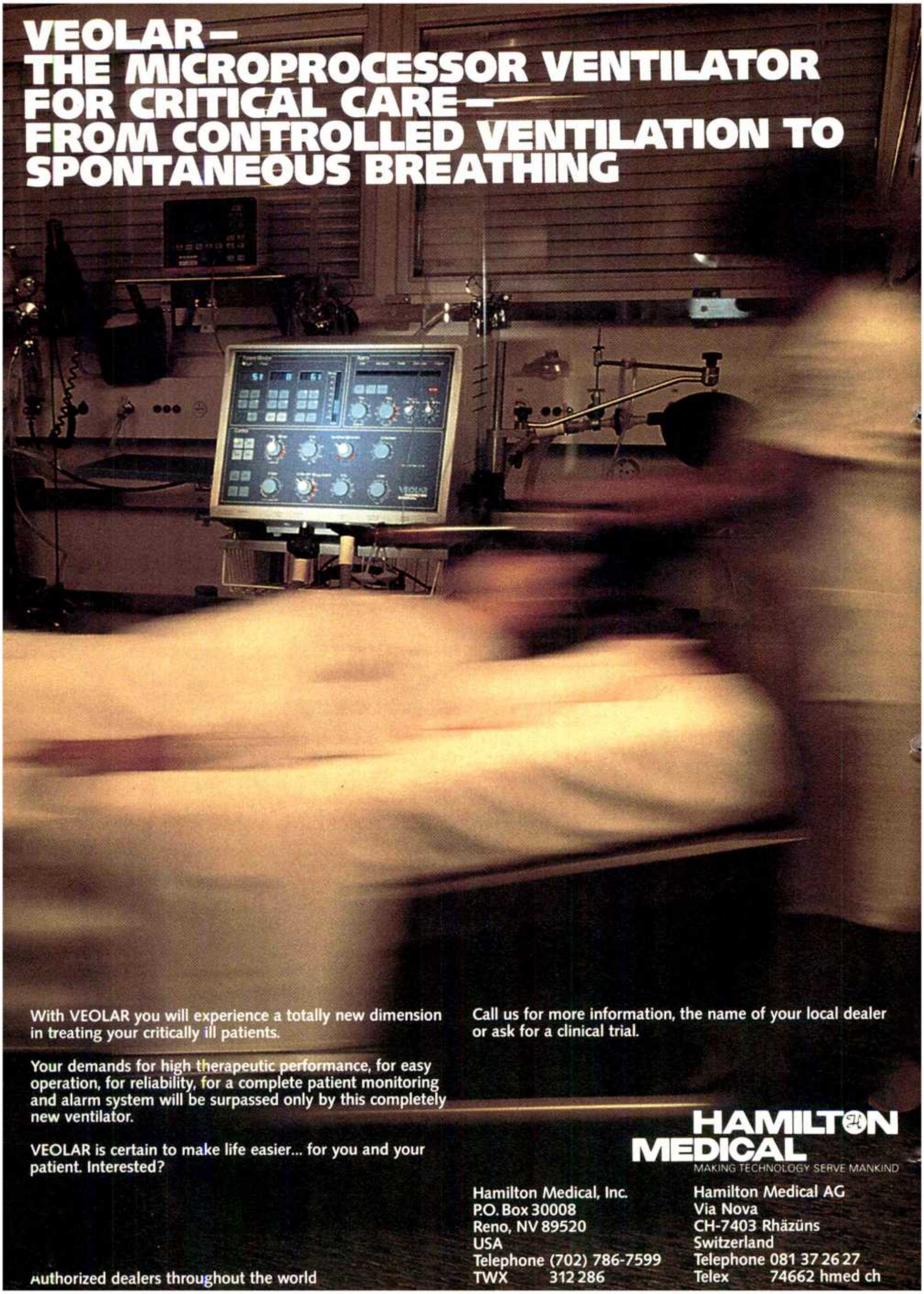

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EDITORIAL

ACUTE/ADULT/ANIMAL RESPIRATORY DISTRESS SYNDROME

A Sideways look at ARDS

Almost 20 years ago an article, appearing in *The Lancet* (Ashbaugh et al., 1967), described life threatening acute respiratory distress in 12 patients. The respiratory failure appeared to be a consequence of a separate non-lung trauma. The patients were commonly markedly dyspnoeic, with evidence of increased respiratory effort, arterial hypoxaemia refractory to increasing the inspired oxygen concentration and diffuse pulmonary infiltrates on the chest radiograph, strongly implying that pulmonary oedema had developed.

Three years later it became possible to measure an index of left heart filling pressures using flow-directed pulmonary artery catheters (Swan et al., 1970). With this information it was soon obvious that the patients with acute respiratory distress had pulmonary oedema in the presence of a low pulmonary artery occlusion pressure. Postmortem lung morphology from these patients revealed congested lungs with hyaline membranes (Petty and Ashbaugh, 1971). Acute respiratory distress was transformed by this latter article to Adult Respiratory Distress Syndrome. Patients no longer had an unexplained and obscure form of heart failure, but had non-cardiogenic pulmonary oedema and respiratory failure secondary to a non-pulmonary cause. The stage was set for an explosion of papers and case reports which attempted to investigate any and all of the causal relationships and reasons behind the development of Adult RDS. It rapidly became obvious that to find a non-pulmonary medical condition not associated with Adult RDS would be far more difficult. Indeed, the only notable absence from the lists was the connection between Adult RDS and sexual practices—either normal or abnormal. The AIDS pandemic will surely provide the data necessary to fill this gap.

A number of aspects of this syndrome are worth highlighting. First, the lack of a universally acceptable definition of Adult RDS. The diagnosis of Adult RDS is usually based on having five prerequisites:

(1) Respiratory failure requiring mechanical ventilation.
(2) Bilateral diffuse infiltrates on the chest radiograph.
(3) A low total respiratory system compliance.
(4) Arterial hypoxaemia, refractory to increased inspired oxygen.
(5) A low pulmonary artery occlusion pressure.

It is worth noting that only (2) and (4) were part of the original acute respiratory distress syndrome and that there is no consensus as to the numerical values representing abnormality of any of the measurable variables. Nevertheless, these variables became the standard accepted for publication; without these data the patient has not got publishable Adult RDS (PARDS).

Second, the ability to define PARDS opened the door to investigations of the effects of treatment. A number of the studies published in the early 1970s suggested that mechanical ventilatory support itself, and later extracorporeal membrane oxygenator (ECMO) support, did not improve the outcome of patients with PARDS. These data led to the notion that, if supportive care was unable to improve outcome, then the alternative must be to highlight the mediators and modulators of the underlying disease process and, thereby, define specific pharmacological treatment. It was obvious that a model of lung injury was needed to characterize the complex pathophysiology of the lesion; but which lesion? To recapitulate, the patients with PARDS have non-cardiogenic pulmonary oedema. This suggests that at some time there is an increase in the leakiness of the lung microvascular membrane to solutes, especially proteins, and water. The most popular animal model for studies of lung injury leading to increased microvascular permeability is lung lymph collection in the sheep. In this species lung lymph can be collected and analysed for protein content. An increase in lymph flow without a decrease in protein concentration means protein clearance from the lung has increased and this event is taken as an index of increased microvascular permeability. Despite this model being originally developed as a means of investigating the physiology of oedema formation (Staub, 1974), it has become the gold standard for investigating lung injury leading to Animal RDS.

As patients with sepsis are reported to be at especially high risk of developing PARDS and also Multiple Organ Failure Syndrome (MOFS) (Carrico et al., 1986), considerable effort has gone into defining the mechanisms and treatment of increased lung permeability in sheep given i.v. endotoxins. Indeed, pretreatment with corticosteroids (Brigham, Bowen and McKeen, 1981) will abolish the increase in lung lymph protein clearance in sheep given endotoxin. We have now convincing evidence for a treatment of Animal RDS. So why is the problem still with us, and why do about 5–8% of patients admitted to intensive care units and requiring ventilatory support fulfil the constellation of criteria for ARDS (Fein et al., 1983; Searle, 1985)? Possibly more important, why are a large proportion of these patients still dying?

A number of reasons may be put forward. First, it may be that PARDS is diagnosed in the most severely ill patients and is very difficult to treat, whereas a less severe form of the same process (Acute RDS) may be more amenable to simple ventilatory support. It is well recognized that the entry criteria for the ECMO study in the U.S.A. were extremely stringent, which may account for the virtual 100% mortality in both the ECMO and conventionally managed control groups. Most intensive care units admit patients with a gradation of respiratory insufficiency; not all have PARDS. It has been suggested recently that the inclusion of only patients with PARDS, but excluding those with acute RDS, may severely bias the results of studies investigating the efficacy of treatment schedules (Rinaldo, 1986).

Second, all that is PARDS may not be excessively leaky! While capillary leak is well described, is it a universal fact in patients with PARDS? Earlier studies produced convincing evidence to show that the ratio of protein concentration in oedema fluid to plasma was higher in patients without than with cardiogenic pulmonary oedema (Sprung et al., 1981). However, this result was brought about mainly because of a lower plasma protein concentration in the non-cardiac oedema group, the protein concentrations in the oedema fluid between the two, supposedly, different aetiologies being almost identical. More recently, studies at the Hammersmith Hospital have investigated patients with PARDS and showed that not all patients had demonstrable protein leakage (using the rate of pulmonary accumulation of radiolabelled transferrin (Braude et al., 1986)), nor was the clearance from the lung of aerosolized ^{99m}Tc-DTPA (Royston, 1985) universally abnormal, despite the latter technique being highly sensitive to otherwise minor pertubations.

If lung microvascular protein leakiness cannot be demonstrated in certain patients, then it is logical that treatments aimed at reducing the inflammation and permeability defect would appear to have little effect.

Finally, the enthusiasm for trying to prevent the deleterious effects of endotoxaemia on the lung based on the Animal RDS studies should be tempered with some caution, for a number of reasons. While steroids prevent lung injury in Animal RDS, this treatment may induce a degree of immunosuppression leading to secondary infections, with further endotoxaemia. Evidence to support this hypothesis comes from recently reported studies (Weigel et al., 1985) in which patients at risk of developing Adult RDS were treated with steroids before respiratory failure developed. The group given steroids had an increased mortality from infection, with no decrease in the incidence of ARDS. Similarly, the recent literature reports instances of sepsis-associated MOFS with a stable or improved pulmonary status (Bell et al., 1983) implying that the improved pulmonary function was at the expense of a secondary lethal infection. Finally, while the administration of endotoxin produces profound pulmonary effects in sheep, these effects are difficult if not impossible to reproduce in other species such as rodents or rabbits.

In conclusion, Adult Respiratory Distress Syndrome implies a diagnosis for publications not patients. The use of the term suggests an underlying pathology which may not be demonstrable. Are we looking for the magic bullet treatment which answers the wrong question in the wrong models? It has been suggested that the term Adult Respiratory Distress Syndrome be allowed to rest in peace (Murray, 1975), the alternative being to describe the respiratory insufficiency as being associated with a predisposing cause. It is now possible to include in this description a measure of both the presence and degree of protein leakage into the lung. This approach may lead to the definition of subgroups of patients with lung injuries which are completely amenable to specific therapy and a recognition of those groups which are more difficult to treat and on whom our efforts can be focused. In the meantime, the term ARDS has come to have little use and less meaning.

D. Royston

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PHARMACOKINETICS OF ATRACURIUM IN ANAESTHETIZED INFANTS AND CHILDREN

B. W. BRANDOM, R. L. STILLER, D. R. COOK, S. K. WOELFEL,
S. CHAKRAVORTI AND A. LAI

SUMMARY

The pharmacokinetics of atracurium were studied in infants and children anaesthetized with isoflurane and nitrous oxide in oxygen. There were no significant differences in volume of distribution (area) (139 v. *152 ml kg*$^{-1}$*), clearance (5.1* v. *5.3 ml kg*$^{-1}$ *min*$^{-1}$*),* $T_{\frac{1}{2}}^{\alpha}$ *(2.1* v. *2.0 min), or* $T_{\frac{1}{2}}^{\beta}$ *(19.1* v. *20.3 min) between children with normal hepatic and renal function and those with moderately impaired hepatic function presenting for hepatic transplantation. There were significant differences in volume of distribution (area) (176* v. *139 ml kg*$^{-1}$*) and in clearance of atracurium (9.1* v. *5.1 ml kg*$^{-1}$ *min*$^{-1}$*) between infants and children with normal excretory function. In infants the clearance of atracurium in ml m*$^{-2}$ *min*$^{-1}$ *(153* v. *133) tended to be greater and the* $T_{\frac{1}{2}}^{\alpha}$ *and* $T_{\frac{1}{2}}^{\beta}$ *tended to be shorter (1.0* v. *2.0 and 13.6* v. *19.1) than in children with normal excretory function; however, these trends did not reach statistical significance. Plasma laudanosine concentration was around 100 ng ml*$^{-1}$ *greater in patients with liver disease than in normal children from 15–45 min following a bolus of atracurium 0.5 mg kg*$^{-1}$*.*

Atracurium, a non-depolarizing neuromuscular blocking drug with an intermediate duration of action, is metabolized by non-specific esterases and decomposes spontaneously via Hofmann elimination (Basta et al., 1982; Merrett, Thompson and Webb, 1983). *In vitro* about two-thirds of atracurium is degraded by ester hydrolysis and one-third by the Hofmann reaction (Stiller, Brandom and Cook, 1985; Stiller, Cook and Chakravorti, 1985). Thus, each pathway plays an important role in the degradation of atracurium; laudanosine is the major end product of each pathway. Neither true- or pseudo-cholinesterase has any effect on the inactivation of atracurium, and the nature of the non-specific esterases has been poorly defined. In patients with liver disease, esterase activity may be reduced, the protein binding of drugs may be affected, body fluid compartments may be altered, and the renal excretion of drugs decreased (Duvaldestin et al., 1978). These changes could affect the pharmacokinetics of atracurium.

In addition, age-related differences in dose requirements and duration of action of atracurium between infants, children and adults have been reported (Brandom, Rudd and Cook, 1983; Brandom et al., 1984). Since these changes could be the result of age-related alterations in either the pharmacokinetics or pharmacodynamics of atracurium, we have studied the pharmacokinetics of atracurium in infants and in children with normal or abnormal liver function.

PATIENTS AND METHODS

Two groups of eight children aged between 2 and 10 yr, inclusive, and one group of six infants aged between 1 and 8 months, inclusive, were studied.

Barbara W. Brandom, m.d.; Richard L. Stiller, ph.d., D. Ryan Cook, m.d.; Susan K. Woelfel, m.d.; Sephali Chakravorti, ph.d.; Allen Lai, ph.d.; Departments of Anesthesiology, Children's Hospital of Pittsburgh and University of Pittsburgh, Pittsburgh, PA and the Clinical Research Division, Burroughs Wellcome Co. Research Triangle Park, North Carolina, U.S.A.

Correspondence to B. W. B., Department of Anesthesiology, Children's Hospital of Pittsburgh, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213–3417, U.S.A.

TABLE I. *Laboratory evaluation of children (mean ± SEM).* $^{*}P < 0.05$

	Normal liver function ($n = 8$)	Impaired liver function ($n = 8$)
PT (s)	12.9 ± 0.3	16.2 ± 2.5
PTT (s)	23.6 ± 1.1	33.6 ± 5.8
Total bilirubin (mg dl^{-1})	0.9 ± 0.5	18.7 ± 5.7*
Alkaline phosphatase (iu)	148.3 ± 34.8	406.8 ± 88.0*
GGT (iu)	19.4 ± 7.1	542.0 ± 261.6
SGOT (iu)	24.5 ± 2.2	207.4 ± 43.3*
SGPT (iu)	16.1 ± 3.4	178.8 ± 40.5*
Albumin (g dl^{-1})	3.0 ± 0.3	3.4 ± 0.3

All patients were about to undergo surgical procedures during which tracheal intubation and the monitoring of intra-arterial pressure would be beneficial. The study was approved by the institutional review board and informed consent was obtained from a parent. The control group of children had a mean age of 6.1 yr (±1.1 SEM), body weight 24.8 kg (±5.5), and a body surface area 0.9 m^2 (±0.13). These patients had normal hepatic and renal function and acid–base balance was normal. The children with liver disease had a mean age of 3.3 yr (±0.6), weight of 15.3 kg (±1.4) and a surface area of 0.62 m^2 (±0.04). Children in the control group were older ($P < 0.05$) and tended to be larger (as reflected by weight and surface area) than those with liver failure, but all children in both groups were near the 50th percentile (±13) by weight for their age. Three of the patients with liver disease had chronic rejection of transplanted livers and five had biliary atresia with failed Kasai procedures and evidence of portal hypertension; all were producing urine in clinically adequate volumes. Prothrombin and partial thromboplastin times, and total bilirubin, alkaline phosphatase, GGT, SGOT, SGPT and albumin concentrations were obtained in both groups of children at the time of the study (table I). Patients requiring liver transplantation had statistically significant increases in the total bilirubin, alkaline phosphatase, SGOT, and SGPT concentrations ($P < 0.05$); GGT concentration tended to be lower in the control patients. Thus, these patients had moderate to severely impaired hepatic function (Class B–C of Child's classification) (Child, 1964).

The infants had a mean age of 5.5 months (±1.1), weight 5.1 kg (±0.7), and a surface area 0.29 m^2 (±0.25). They were presenting for a variety of cardiovascular or pulmonary procedures; all were producing urine in clinically adequate volumes.

General anesthesia was induced in all patients with either nitrous oxide and isoflurane in oxygen (by inhalation) or thiopentone 4–7 mg kg^{-1} i.v.; anaesthesia was maintained with nitrous oxide and isoflurane (1% end-tidal) in oxygen during the placement of intravascular catheters. Fentanyl 3–5 µg kg^{-1} was given as a supplement, if needed.

Atracurium 0.5 mg kg^{-1} was administered i.v. over 10 s. Heparinized arterial blood samples (1–2 ml) were drawn at 1.5, 3, 5, 7.5, 10, 15, 30, 45 and 60 min after the bolus was given. If clinically necessary, additional doses of fentanyl or a dose of pancuronium 0.1 mg kg^{-1} were given during this period. These drugs have been shown not to interfere with the assay of atracurium. Because of the time required for the positioning of the patient and preparation of the skin, little blood loss and only minimal cardiovascular change occurred during the period of arterial blood sampling. The blood sample was promptly dispensed into polypropylene vials and spun in an Eppendorf Model 5412 high-speed centrifuge for 20 s. Plasma was transferred quickly into another polypropylene vial containing 3N HCl 0.01 ml and frozen in dry ice–acetone slush (−70 °C). Measurement of the concentrations of atracurium and laudanosine was by specific high pressure liquid chromatography (Stiller, Brandom and Cook, 1985).

The plasma atracurium concentration against time curve for each patient was fitted to a two-compartment exponential equation using a non-linear least square analysis adapted from Yamaoka, Tanigowakay and Uno (1981). From the macrokinetic parameters (A,α, B,β) the volume of the first compartment (V_1), volume of distribution (area) ($V\mathrm{D}^{\mathrm{area}}$), plasma half-lives ($T_{\frac{1}{2}}^{\alpha}$ and $T_{\frac{1}{2}}^{\beta}$) and plasma clearance (*Cl*) were determined from standard formulae as used by Ward and Neill (1983). Since the elimination of atracurium is presumed to be from both compartments, estimation of microkinetic constants is impossible. The volumes and clearance were expressed in terms of both body weight and surface area.

The pharmacokinetic variables for the two groups of children, and the normal children *v.* the

TABLE II. *Atracurium pharmacokinetics in children ($mean \pm SEM$)*

	Normal liver function ($n = 8$)	Impaired liver function ($n = 8$)
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.1 ± 0.2	2.0 ± 0.2
$T_{\frac{1}{2}}^{\beta}$ (min)	19.1 ± 1.6	20.3 ± 1.4
V_1 (ml kg^{-1})	52.6 ± 2.0	46.0 ± 2.6
$V\text{D}^{\text{area}}$ (ml kg^{-1})	139.0 ± 8.3	152.2 ± 9.1
Cl (ml kg^{-1} min^{-1})	5.1 ± 0.2	5.3 ± 0.4
$V\text{D}^{\text{area}}$ (ml m^{-2})	3509.5 ± 236	3729.6 ± 340
Cl (ml m^{-2} min^{-1})	133.4 ± 14.3	128.7 ± 11.3

TABLE III. *Atracurium pharmacokinetics in infants* ($n = 6$) ($mean \pm SEM$). **Significantly different than children (table II)*

$T_{\frac{1}{2}}^{\alpha}$ (min)	1.0 ± 0.2
$T_{\frac{1}{2}}^{\beta}$ (min)	13.6 ± 0.6
V_1 (ml kg^{-1})	50.55 ± 2.6
$V\text{D}^{\text{area}}$ (ml kg^{-1})	176.7 ± 9.1*
Cl (ml kg^{-1} min^{-1})	9.1 ± 0.7*
$V\text{D}^{\text{area}}$ (ml m^{-2})	2994.0 ± 136.3
Cl (min m^{-2} min^{-1})	153.2 ± 9.6

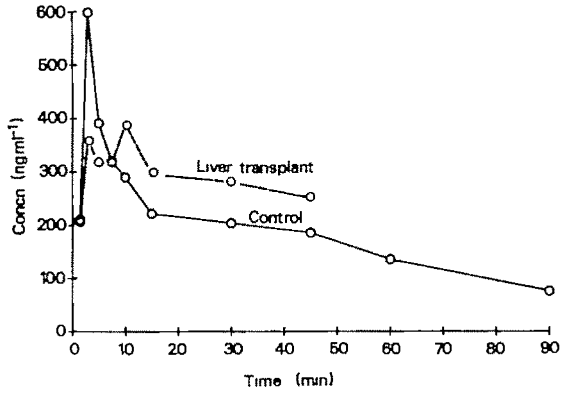

FIG. 1. Mean plasma laudanosine concentrations (ng ml^{-1}) over time in normal children and those with liver failure following a bolus of atracurium 0.5 mg kg^{-1}.

infants, were compared by Student's t test or the Mann–Whitney test where appropriate. Differences were considered significant when $P < 0.05$. Two-tailed tests were used.

RESULTS

There was no difference in the pharmacokinetic variables when expressed in terms of either weight or surface area between the two groups of children (table II). When the infants were compared with the control children, the α and β half-lives tended to be shorter, clearance (ml m^{-2} min^{-1}) tended to be more rapid, and there were significant differences in the volume of distribution (ml kg^{-1}) and in clearance (ml kg^{-1} min^{-1}) (table III). Volume of distribution (area) (ml m^{-2}) was similar in infants and children.

Laudanosine was detectable in the plasma in all patients studied. However, the shape of the laudanosine concentration–time curve was different in the two groups of children. In children without liver disease, laudanosine concentrations peaked early (within 3–4 min), reaching approximately 600 ng ml^{-1}, and then decreased (fig. 1). In patients with liver disease, two peak plasma laudanosine concentrations were observed; however, the maximum plasma laudanosine concentrations reached was no more than 400 ng ml^{-1}. The rate of decline of plasma laudanosine concentrations in the patients with liver failure appeared to parallel that in the children without liver disease.

DISCUSSION

This study was designed to assess the influence of both liver function and age on the pharmacokinetics of atracurium. Atracurium is not significantly metabolized in or excreted through the liver, nor cleared through the kidney. Thus, conceptually, atracurium is internally cleared through ester hydrolysis and Hofmann elimination. In this study moderate to severely impaired liver function had no effect on the kinetics of atracurium; clearance and the volume of distribution were similar in the normal and in the patients with liver failure. Hence, $T_{\frac{1}{2}}^{\beta}$ was similar. Ward and Neill (1983) evaluated the kinetics of atracurium in adults with acute hepatic failure self-induced by paracetamol. In their study the volume of distribution of atracurium was statistically larger in the patients with liver failure than in normal patients, and the clearance of atracurium tended to be greater in these patients. Because of the relationship between these variables, $T_{\frac{1}{2}}^{\beta} = 0.693\ V\text{D}/Cl$, changes in the volume of distribution ($V\text{D}$) and in clearance (Cl) can offset one another and result in similar $T_{\frac{1}{2}}^{\beta}$. In patients hypoproteinaemic from severe chronic liver disease, pseudocholinesterase activity, coagulation factors and drug metabolizing activity may be limited (Duvaldestin, Lebrault and Chauvin, 1983). Although the kinetics of atracurium have not been studied in such patients, one suspects that non-specific esterase activity and, hence, the metabolism of atracurium may be severely limited.

Changes in the volume of distribution, protein binding and kinetics have been noted for other myoneural blockers in patients with moderate liver disease. For example, the metabolism and biliary excretion of pancuronium and vecuronium are decreased in patients with liver disease (Duvaldestin, et al., 1978; Somogyi, Shanks and Triggs, 1977; Duvaldestin et al., 1982). Thus, only extremely severe liver disease has any potential influence on the kinetics of atracurium; renal disease has no influence (Fahey et al., 1984). Although the kinetics of atracurium are normal in patients with renal and liver failure, laudanosine tends to accumulate in such patients. This is not unexpected, since laudanosine is excreted by the kidney and metabolized by the liver (Fahey et al., 1984; Sharma et al., 1984). The secondary peaks of laudanosine seen in our patients with liver failure may be a reflection of alternative routes of atracurium metabolism.

The infants tended to have shorter α and β half-lives than the children; the volume of distribution and the clearance (ml kg^{-1}) were significantly greater in infants than in children. If the $T_{\frac{1}{2}}^{\beta}$ were constant, the clearance of atracurium would be linearly related to the volume of distribution with a slope of $0.693/T_{\frac{1}{2}}^{\beta}$. The correlation coefficient between clearance (ml kg^{-1} min^{-1}) and volume of distribution (ml kg^{-1}) was 0.68 in our normal infants and children. Age-related differences in the extracellular fluid volume are mirrored by differences in the volume of distribution for other blocking agents (for example, tubocurarine and vecuronium) (Fisher et al., 1982; Fisher, Castagnoli and Miller, 1985). Specifically, infants have a large extracellular fluid volume (ml kg^{-1}) and a large volume of distribution for myoneural blocking drugs. Indeed, the volume of distribution of atracurium decreased with advancing age ($r = -0.73$); clearance, likewise, decreased with age ($r = -0.60$); $T_{\frac{1}{2}}^{\beta}$ did not correlate with age. In contrast to those of tubocurarine and vecuronium, the $T_{\frac{1}{2}}^{\beta}$ of atracurium was not prolonged in infants as the volume of distribution increased. The more rapid elimination half-life and higher clearance of atracurium in infants is consistent with the previously observed shorter duration of neuromuscular blockade in this age group (Brandom et al., 1984). Untested pharmacodynamic differences might also exist.

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USE OF ATRACURIUM DURING MAJOR ABDOMINAL SURGERY IN INFANTS WITH HEPATIC DYSFUNCTION FROM BILIARY ATRESIA

D. A. SIMPSON AND D. W. GREEN

Infants with hepatic dysfunction caused by biliary atresia presenting for the operation of hepaticoportoenterotomy (Kasai operation) pose problems for the anaesthetist which make the selection of an appropriate neuromuscular blocking drug worthy of consideration. The patients are very young (< 2–3 months), as correction before the development of irreversible liver damage improves the prognosis (McClement, Howard and Mowat, 1985). The effects of an immature neuromuscular system (Brandom and Cook, 1985) are worsened by the decrease in respiratory reserve caused by a large abdominal incision, hepatomegaly, ascites and, when required, the transfusion of substantial quantities of blood. Consequently, residual neuromuscular blockade would be most undesirable in the postoperative period. In addition, since the surgical correction involves the anastomosis of a loop of small bowel on to the porta hepatis, it would seem preferable to avoid the potentially harmful effects on the anastomosis associated with the administration of neostigmine (Wilkins et al., 1970).

The unique property possessed by atracurium, of spontaneous degradation at body pH (Hofmann elimination), removes the influence of changes in hepatic metabolism on the antagonism of blockade induced by this drug, and its intermediate duration of action may make it possible to omit the use of antagonist agents altogether.

The aim of this study was to assess the use of atracurium for major abdominal surgery in a group of infants with hepatic dysfunction.

SUMMARY

The use of atracurium during major abdominal surgery was assessed in 20 infants with hepatic dysfunction caused by biliary atresia. An initial dose of 0.6 mg kg^{-1} *provided excellent intubating conditions in all patients. Subsequent neuromuscular blockade was monitored with a peripheral nerve stimulator and incremental doses of atracurium were given on reappearance of a single twitch. Neuromuscular conduction was allowed to return at the end of surgery and by careful timing of increments it was necessary to antagonize the neuromuscular blockade in only two patients.*

PATIENTS AND METHODS

Twenty consecutive patients (11 male) who were about to undergo hepaticoportoenterotomy entered the study. All had been extensively evaluated in the preoperative period. Premedication consisted of atropine 0.1 mg i.m. given 30–60 min before surgery.

On arrival in the operating theatre, the patient was placed on a warming blanket on the operating table and connected to an electrocardiograph. Anaesthesia was induced by the inhalation of 2–3 % halothane and nitrous oxide in 30 % oxygen via a Jackson–Rees modification of Ayre's T-piece. Once the patient was asleep, an arterial pressure cuff was placed on the right arm and two small self adhesive ECG electrodes were fixed over the median nerve at the elbow. These allowed for subsequent monitoring of neuromuscular blockade via a portable peripheral nerve stimulator (Ministim R) using "train-of-four" stimuli with a frequency of 2 Hz; the resultant twitches were assessed visually.

D. A. SIMPSON, M.B., F.F.A.R.C.S.; D. W. GREEN, M.B., F.F.A.R.C.S.; Department of Anaesthetics, King's College School of Medicine and Dentistry, Denmark Hill, London SE5 9RS.

An i.v. infusion was commenced and after the position of the stimulating electrodes had been verified, atracurium 0.6 mg kg^{-1} was administered. The trachea was intubated when no twitches were visible, and the lungs ventilated with humidified nitrous oxide and 0.5–1% halothane in oxygen using a Vickers "Neovent" ventilator. Blood loss was measured by the weighing of swabs, and was replaced accordingly. Rectal temperature was monitored throughout the operation.

Incremental doses of atracurium were given as soon as the first twitch reappeared, and the times of administration noted. No further increments were given after the closure of the peritoneum. Immediately before extubation, the train-of-four was assessed and, unless the fourth twitch was significantly less than the first on visual scoring, the residual neuromuscular blockade was not antagonized. The trachea was extubated once the patient was awake. If there was any doubt as to the adequacy of neuromuscular function (either clinically or by train-of-four ratio), atropine 0.03 mg kg^{-1} and neostigmine 0.06 mg kg^{-1} were given i.v. A recording of the integrated electromyographic response to peripheral nerve stimulation was obtained in two patients (Datex Relaxograph) to provide a more accurate monitor of neuromuscular blockade and support the method of visual scoring. The increments for these patients were still given according to the previous criteria.

TABLE I. *Characteristics of patients studied (mean values $\pm$ SD, range in parentheses)*

No. patients	20	(9F/11M)
Age at operation (days)	71 $\pm$ 22	(26–106)
Weight (kg)	4.6 $\pm$ 0.9	(3.1–6.2)

TABLE II. *Preoperative liver function tests*

Investigation	Mean	SD	Range	Normal values
Total protein (g litre^{-1})	57	4	51–65	60–80
Albumin (g litre^{-1})	38	4	31–44	35–50
Bilirubin (µmol litre^{-1})	158	58	75–332	3–20
Gamma GT (iu litre^{-1})	834	403	103–1629	0–45
AST (iu litre^{-1})	259	89	103–476	7–40
Alkaline phosphatase (iu litre^{-1})	834	561	375–2581	30–85

TABLE III. *Doses of atracurium used. †18 patients; ‡12 patients*

	Mean	SD	Range
Initial dose (mg kg^{-1})	0.6		
Time (min):			
To 1st increment	43	10	30–65
1st–2nd increments†	31	5	19–42
2nd–3rd increments‡	32	8	21–46
Last top-up to extubation	44	10	25–60
Duration of surgery (min)	133	48	110–192

RESULTS

The characteristics of the 20 patients studied are shown in table I.

Preoperative liver function tests were all indicative of hepatic dysfunction, with marked increases in the serum bilirubin concentration, and in the concentrations of the liver enzymes (table II).

Following the initial dose of atracurium of 0.6 mg kg^{-1}, intubation of the trachea was possible within 3 min, by which time no twitch was visible on train-of-four stimulation. The conditions for intubation were considered to be excellent in all patients. The first incremental dose was required by all patients and was given on average ($\pm$SD) at 43 $\pm$ 10 min (range 30–65 min). The dose administered was usually 1 mg (0.5 or 0.75 mg for the smaller infants). Eighteen patients required a second, and 12 patients a third increment, and the interval between these doses was consistent at 31 $\pm$ 5 and 32 $\pm$ 8 min, respectively. Four patients, in whom surgery was prolonged, required more than three increments; subsequent doses were given at similar intervals.

The total dose of atracurium used was 5.1 $\pm$ 1.4 mg (range 2.75–8 mg) with a duration of surgery (from time of first dose of atracurium to extubation) of 133 $\pm$ 48 min. The dose of atracurium was also calculated in mg kg^{-1} h^{-1} and this value was remarkably consistent at 0.45 $\pm$ 0.1 mg (range 0.33–0.68 mg) (table III).

The interval between the last dose of atracurium and the end of the operation was 44 $\pm$ 10 min (range 25–60 min), and only two patients required formal antagonism of neuromuscular blockade with atropine and neostigmine—although relaxation was considered adequate by the surgeon. Evidence that reversal had occurred spontaneously was obtained using the nerve stimulator (as

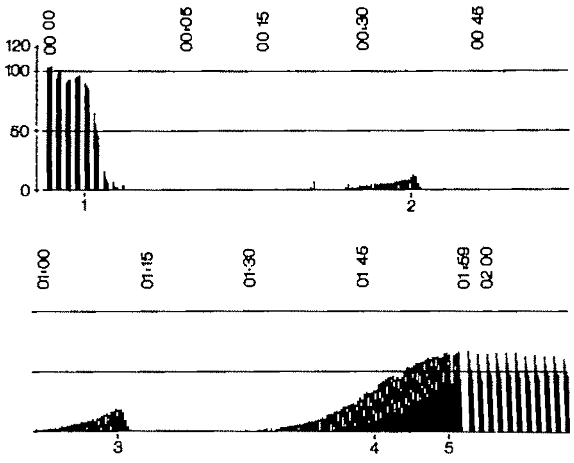

FIG. 1. Individual tracing of neuromuscular blockade.

Mark		Time	T1%	T1/ T4%
1	Initial atracurium 2.5 mg	10.49	100	100
2	1st increment atracurium 1.0 mg	11.25	15	12
3	2nd increment atracurium 1.0 mg	11.57	18	15
4	Start peritoneum	12.36	30	25
5	Skin closure	12.45	70	70
	Extubation	12.50	70	85

Loss of twitch height during procedure is probably caused by worsening electrode contact.

described above) and the clinical condition of the patient before extubation. In two patients, this method was supplemented with information obtained from the Datex Relaxograph. A printout of one of the resultant electromyograms is reproduced in figure 1.

All patients underwent a Kasai operation and during surgery rectal temperature was maintained between 36.5 and 38 °C. Average (±SD) blood loss was 74±32 ml.

DISCUSSION

In biliary atresia, there is progressive inflammation of the biliary tract, possibly a type of sclerosing cholangitis, which usually starts extrahepatically and then spreads to involve all of the bile duct system (Howard, 1983). The aetiology of extrahepatic biliary atresia remains obscure and the majority of untreated patients die from cirrhotic liver failure before 2 years of age. Surgical treatment at King's College Hospital follows the approach first described by Kasai and Suzuki (1959). The obliterated extrahepatic ducts are excised at the level of the porta hepatis which leaves bile to drain from minute residual channels. A Roux-en-Y loop of jejunum is then anastomosed to the cut surface. Frequently, it is necessary to resect a portion of liver to allow suitable access.

The hepatic dysfunction seen in these patients is mainly of the cholestatic type as reflected by the marked increases in the concentrations of alkaline phosphatase and gamma GT (table II). As the untreated infants age, progressive hepatocellular damage ensues as indicated by the increased transaminase (AST) concentrations. However, this could not have been severe in the patients studied since the albumin concentration was still normal.

Many commonly used non-depolarizing neuromuscular blocking agents are partly metabolized in the liver and thus one would expect their duration of action to be prolonged in patients with hepatic dysfunction. There may also be apparent resistance to these drugs, requiring a larger initial dose in these subjects. This has been observed for tubocurarine (Dundee and Gray, 1953) and pancuronium (Ward, Adu-Gyamfi and Strunin, 1975). The latter effect is probably caused by a large volume of distribution, as has been shown for pancuronium by Westra and colleagues (1981). This larger volume of distribution will also increase the elimination half-life of the drug, even if the plasma clearance proceeds at the same rate.

In contrast, Ward and Neill (1983) have shown that the pharmacokinetics of atracurium were unaffected by hepatic failure and this has been confirmed in children (Cook et al., 1984). In addition, Brandom and coworkers (1984) noted that the recovery of neuromuscular function following atracurium was quicker in infants (2–6 months of age) than in adult patients. Thus atracurium would seem to be the ideal non-depolarizing neuromuscular blocker for procedures on infants with hepatic dysfunction who require profound neuromuscular blockade.

Selection of a relatively large initial dose of atracurium (0.6 mg kg^{-1} or four times the ED_{95}) was determined by the following factors:

(1) Duration of surgery: since most Kasai operations exceed 120 min, a large initial dose would seem appropriate.

(2) Lack of agreement on the ability of

0.3 mg kg^{-1} (Brandom et al., 1984) or 0.4 mg kg^{-1} (Goudsouzian et al., 1985) to produce excellent intubating conditions in patients of similar age.

(3) The apparent lack of histamine release or cardiovascular effects of atracurium in infants, even at four times the ED_{95} (Brandom and Cook, 1985).

In this study, intubating conditions were excellent in all patients and there was no clinical evidence of histamine release or cardiovascular dysfunction.

After the intubating dose, there was some variation between patients in the time until the return of the first twitch and, thus, between the subsequent incremental doses (table III). The mean intervals between these were 43 ± 10 min, 31 ± 5 min and 32 ± 8 min, respectively. We consider this represents good clinical predictability for this class of drug. The total requirements of atracurium also showed consistency at 0.45 ± 0.1 mg kg^{-1} h^{-1}. Using the nerve stimulator in the way described, reliable information was obtained easily as to the degree of paralysis in each patient, and allowed the appropriate administration of incremental doses.

It proved necessary to antagonize neuromuscular blockade in two patients using the T4:T1 ratio obtained from the visual score. Previous studies in adults (Ali, Utting and Gray, 1971a, b; Ali et al., 1975) have shown electromyographically and mechanically that the T4:T1 ratio is an accurate measurement of recovery from neuromuscular blockade and that it correlated well with the depression of respiratory function caused by residual paralysis. A ratio of 0.5–0.7, together with clinical evidence of return to "normal" neuromuscular function would seem adequate to allow extubation of the trachea without formal antagonism with neostigmine (Brandom and Cook, 1985).

In summary, it has been shown that atracurium is a suitable non-depolarizing neuromuscular blocking drug for major abdominal surgery in infants with hepatic dysfunction caused by biliary atresia. Its clinical effect was predictable and, with the aid of a nerve stimulator, it was possible to titrate dose to effect and avoid unnecessary antagonism with neostigmine.

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PHARMACOKINETICS OF MORPHINE IN TWO CHILDREN BEFORE AND AFTER LIVER TRANSPLANTATION

M. P. SHELLY, E. P. CORY AND G. R. PARK

SUMMARY

Plasma morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations were measured (HPLC) in two children immediately before orthotopic liver transplantation and in the postoperative period. Both of the patients had end-stage hepatic failure, but one also had impaired renal function before operation and was oliguric during and after surgery. Both patients metabolized morphine rapidly, but in the patient with renal failure, the metabolites appeared to accumulate. Morphine has active metabolic products and the accumulation of these in patients with impaired renal function may lead to a clinically observable prolongation of its effect.

Morphine is metabolized by the liver (Stanski, Greenblatt and Lowenstein, 1978) and the metabolites excreted by the kidney. Recent advances in the estimation of morphine have, however, led to the emphasis being placed on the importance of its elimination by the kidney (McQuay and Moore, 1984a; Moore, Sear and Baldwin, 1984). Renal failure has long been known to prolong the action of morphine, and although this aspect has now been investigated further (Aitkenhead et al., 1984; Ball et al., 1985; Shelly and Park, 1985), the cause of the prolonged action remains obscure. In particular, the role of morphine metabolites has yet to be clarified. Morphine has a number of active metabolites, including morphine-6-glucuronide (Shimomura et al., 1971) and normorphine (Lasagna and De Kornfield, 1958; Johannesson and Milthers, 1962); the 3-glucuronide is thought to be inactive when administered parenterally (Sasajima, 1970; Shimomura et al., 1971). Initially, this was a pilot study to investigate the role of biliary excretion in the elimination of morphine, but we wish to report two patients who appear to illustrate the importance of the kidney in the elimination of morphine or its metabolites.

PATIENTS AND METHODS

Approval was obtained from the district Ethics Committee and informed consent was obtained from the parents of two children about to undergo orthotopic liver transplantation. Preoperative details are summarized in table I. Both children had end-stage liver failure unresponsive to other medical and surgical treatment. One had congenital biliary atresia, the other cholestatic jaundice following neonatal hepatitis; both had secondary biliary cirrhosis. Renal function in both patients was thought to be normal in the preoperative period although, in retrospect, patient 2 had unrecognized renal impairment at this time: her

TABLE I. *Details of two children before liver transplantation*

	Patient 1	Patient 2
Age (yr)	3.5	2.5
Sex	M	F
Weight (kg)	14.0	7.5
Diagnosis	Congenital biliary atresia	Neonatal hepatitis + cholestatic jaundice
Bilirubin (mmol litre^{-1})	372	320
Alkaline phosphatase (mmol litre^{-1})	1430	2390
Urea (mmol litre^{-1})	2.2	12.1
Creatinine (µmol litre^{-1})	< 100	60

M. P. SHELLY; G. R. PARK; Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ. E. P. CORY, Bioanalytical Department, Napp Research Centre, Cambridge Science Park, Milton Road, Cambridge.
Correspondence to G.R.P.

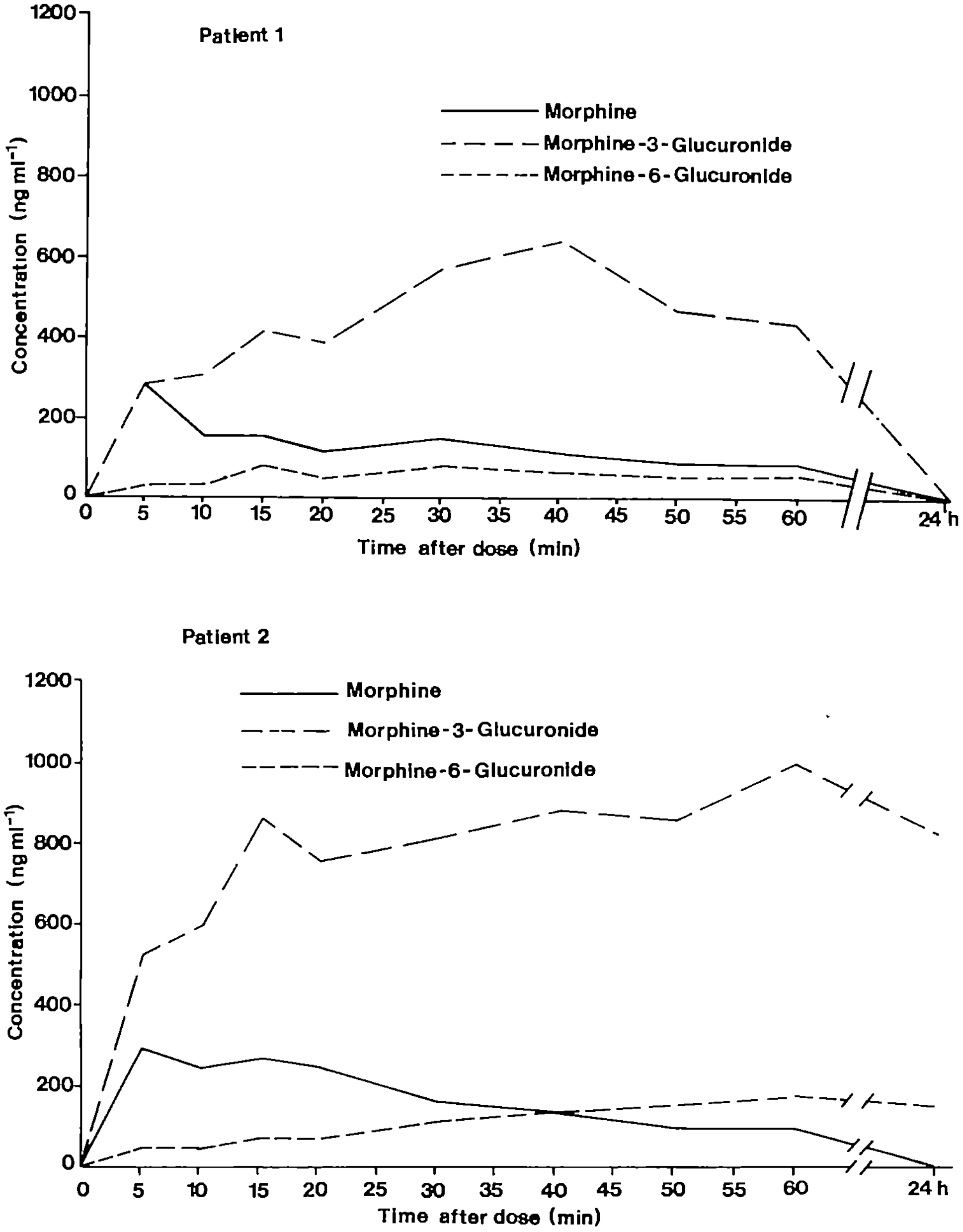

FIG. 1. Plasma morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations in patient 1 and patient 2 during the 60 min immediately before the start of surgery, and at 24 h after the administration of the morphine.

plasma urea concentration was increased although her plasma creatinine concentration was within normal limits.

Anaesthesia was introduced with thiopentone; alcuronium was given to facilitate tracheal intubation and controlled ventilation. Anaesthesia was maintained with halothane and nitrous oxide in oxygen. Following the induction of anaesthesia, but before surgery, a blood sample (baseline) was taken and morphine 1 mg kg $^{-1}$ was administered i.v. as part of the anaesthetic regimen. Further blood samples were taken at 5, 10, 15, 20, 30, 40, 50, 60 min after the administration of the morphine while venous access was secured and monitoring commenced—but before the start of major surgery. Blood removed for sampling was replaced by blood to maintain fluid balance. Further blood samples were taken from each child after surgery.

Plasma morphine, morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) concentrations were measured by high pressure liquid chromatography (HPLC). The standards used were morphine (Evans Medical Ltd, Beaconsfield) and M-3-G (Sigma Chemical Corporation); M-6-G was synthesized using a modification of the technique described by Yoshimura, Oguri and Tsukamoto (1968) and obtained through Napp Research Centre, Cambridge. Samples were prepared in control plasma for calibration, quality control and validation. Calibration curves were constructed for all three compounds.

Solid phase Bond Elut C18 cartridges (Jones Chromatography, Llanbradach, Glamorgan) were used to extract morphine and the two metabolites from plasma. Subsequent quantification was by HPLC using ultraviolet absorption at 210 nm to estimate M-3-G concentrations and electrochemical detection at +0.9 V (*v.* silver–silver chloride) to measure morphine and M-6-G. The lower limit of detection for M-3-G by ultraviolet absorption was 10 ng ml^{-1} and for morphine and M-6-G by electrochemical detection was 1.5 ng ml^{-1}. Recovery from plasma for all three compounds was greater than 90%.

Pharmacokinetic parameters were determined using ESTRIP (Brown and Manno, 1978) to estimate terminal slopes. Clearance was calculated as dose (D) divided by the area under the curve (AUC) where AUC was estimated from the data points by the linear or logarithmic trapezoidal method and extrapolated to infinity. Volume of distribution at steady state was calculated as D.AUMC/AUC^2 where AUMC is the area under the first moment curve, again extrapolated to infinity.

Clinical and biochemical indices of each patient's conscious level, and liver and renal function, as well as their opioid requirement, were recorded before and after surgery.

RESULTS

The plasma concentrations of morphine, M-3-G and M-6-G for both patients are shown in figure 1. During the first 1 h after the induction of anaesthesia, but before the start of major surgery, the plasma concentration of morphine increased initially to high values and then decreased rapidly in both patients. The pharmacokinetic parameters of morphine were: in patient 1, half-life 0.4 h, volume of distribution at steady state 4.4 litre kg^{-1} and clearance 93 ml min^{-1} kg^{-1}; in patient 2, half-life 0.52 h, volume of distribution at steady state 3.4 litre kg^{-1} and clearance 68 ml min^{-1} kg^{-1}.

The plasma concentration of M-3-G increased in both patients, but more steeply and to higher values in patient 2. The concentration of M-3-G then decreased in patient 1, whereas it was maintained in patient 2. Plasma M-6-G concentration increased to a peak at approximately 15 min in patient 1 and was maintained at this value subsequently. In patient 2, however, the concentration of M-6-G increased gradually for the first 15 min, but continued to increase thereafter such that at the end of the 1 h the value was higher than that of the morphine base.

Patient 1, 24 h after his original dose of morphine, had no detectable morphine, M-3-G or M-6-G present in his plasma. Patient 2, 24 h after her original dose of morphine, had no detectable morphine base, but the concentrations of M-3-G and M-6-G were unchanged from concentrations measured at 60 min.

Intraoperative details for both patients are shown in table II. The duration of surgery and the blood loss were similar in both patients and both received a large blood transfusion. Patient 2, however, was anuric throughout the operation, whereas patient 1 had an adequate urine output.

The patients' postoperative urine outputs, conscious levels and opioid requirements are shown in figure 2. Patient 1 maintained a urine output of approximately 1 ml kg^{-1} h^{-1}. He required the regular administration of fentanyl, in spite of which he remained difficult to sedate and further morphine was required 26 h after the initial dose to allow satisfactory control of ventilation. Patient 2 continued to have an

TABLE II. *Operative details*

	Patient 1	Patient 2
Duration of surgery (h)	5	5.5
Blood loss (ml kg^{-1})	79	80
Transfusion requirement (ml kg^{-1})	61	100
Urine output (ml kg^{-1})	6.0	0

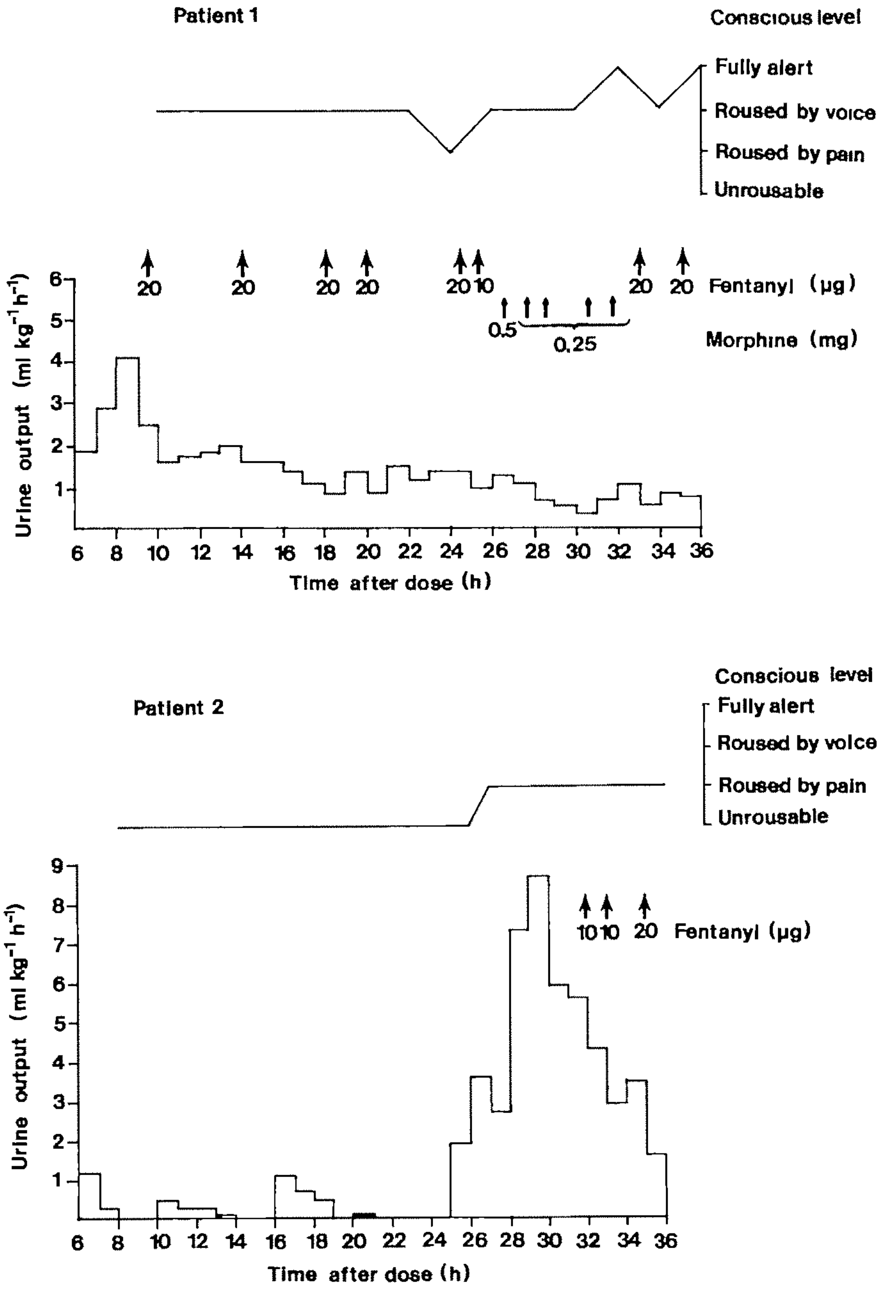

FIG. 2. Postoperative urine output, conscious level and opioid requirement in both patients.

inadequate urine output. In addition, although she received no further opioid, she continued to be unresponsive to painful stimuli and had pin-point pupils throughout this period.

Both patients started to produce bile promptly after surgery and continued to do so, indicating reasonable recovery of liver function.

Patient 2 eventually responded to diuretic therapy and had a large diuresis. One hour after the start of her diuresis, she became responsive to stimuli and her pupils enlarged slightly. Six hours later she required further opioid.

DISCUSSION

Although the liver has long been thought of as the site of morphine metabolism (Stanski et al., 1978), recently, patients with cirrhosis have been shown to eliminate morphine normally (Patwardhan et al., 1981). It has also been suggested that morphine is metabolized in patients with hepatic failure (Hug et al., 1979), but no details were provided of the assay method used to estimate the concentrations of morphine in that study. Extrahepatic sites of morphine metabolism, such as the kidney (McQuay and Moore, 1984b) and the gastrointestinal tract (Park, 1985) have been postulated.

Both the patients described had liver failure during the preoperative period, yet both metabolized morphine rapidly; morphine concentrations decreased and the concentrations of M-3-G and M-6-G increased. Although neither patient was capable of producing bile at this time, the concentrations of morphine decreased. This may refute the importance of the biliary excretion of morphine.

The clearance of morphine in these children was greater than that previously reported in children (Dahlstrom et al., 1979). This may reflect the different methods used to estimate the plasma morphine concentration, or it may result from the relatively short sampling period available in our study before surgery was undertaken with the consequent haemodynamic instability.

The main differences between the two children were their renal function, and their plasma M-3-G and M-6-G concentrations. Patient 1 had normal renal function and had eliminated all detectable morphine, M-3-G and M-6-G by 24 h after the administration of the initial dose. Patient 2 had impaired renal function and a poor urine output. Morphine base was no longer detectable at 24 h, but high concentrations of M-3-G and M-6-G were present in spite of a large intraoperative blood transfusion to replace an operative blood loss approximating to her circulating blood volume. This accumulation of morphine metabolites would appear to indicate that an adequate urine output is important for their elimination. The clinical evidence of recovery in patient 2 when her diuresis started adds support to this hypothesis.

M-3-G is thought to be inactive parenterally, but M-6-G is known to be a powerful analgesic (Shimomura et al., 1971); however, its other actions are unknown. Patient 2 was unresponsive to pain and had pin-point pupils in association with the increased concentrations of M-6-G and this may indicate other opioid-like properties, particularly sedation. This assay method used was calibrated for only M-3-G and M-6-G. Other metabolites which may be active (e.g. normorphine) were not measured.

CONCLUSION

The two patients described illustrate that morphine can be metabolized rapidly, even in the presence of severe liver failure. Impairment of renal function with a low urine output in one of the patients was associated with accumulation of morphine-3-glucuronide and morphine-6-glucuronide and with prolonged narcosis. Morphine has active metabolic products and it may be these that produce the clinically observed prolonged action of morphine in patients with renal failure.

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PROSPECTIVE STUDY OF LIVER FUNCTION IN CHILDREN FOLLOWING MULTIPLE HALOTHANE ANAESTHETICS AT SHORT INTERVALS

H. WARK, M. O'HALLORAN AND J. OVERTON

SUMMARY

In the 4 years January 1981 to December 1984, 186 children received 1362 halothane anaesthetics. Twenty-five patients were anaesthetized with halothane at least 10 times in a year. No patient developed postoperative jaundice. Sixty-nine children were exposed to two halothane anaesthetics within 28 days on 149 occasions and serial estimations of serum liver enzyme concentrations were obtained. Minor increases in the concentrations of serum AST and ALT were recorded in 10.6% and 4.7% of patient entries, respectively. Postoperative GGT and SAP concentrations were increased in 2.7% of patient entries. Patients in whom enzyme values were increased before the first anaesthetic were no more likely than other subjects to develop further changes.

Two retrospective studies have assessed the risk of a child developing postoperative jaundice caused by halothane-associated hepatitis as between 1 in 82000 and 1 in 200000 (Wark, 1983; Warner et al., 1984). The incidence of minor degrees of hepatic dysfunction after halothane anaesthesia in children is unknown.

A prospective study in children was designed to assess the effect, on liver function, of repeated anaesthetics at short intervals. The investigation was performed at the Royal Alexandra Hospital for Children, Sydney between January 1981 and December 1984.

PATIENTS AND METHODS

Multiple halothane anaesthetics within 1 year

Hospital lists were scrutinized for patients having relatively minor surgery in whom multiple exposures to halothane were likely to occur within 1 year. To minimize the effect of surgery on liver function, patients having major abdominal and thoracic surgery were not included. Patients on drugs or treatments known to affect liver function, and patients with severe systemic disease, were excluded also.

Each patient was followed prospectively for 12 months and no new patients were entered into the study after December 1983. If, after the initial 12-month period, it was likely that a patient would receive many further halothane anaesthetics, then the patient was readmitted to the study as a separate entry.

While in hospital, patients were examined daily for the presence of postoperative jaundice. At each outpatient attendance after discharge, the patient's parents were asked about a history of jaundice and the patient was examined for evidence of liver disease.

Effect of repeated halothane anaesthetics within 28 days on tests of liver function

It was considered inappropriate to collect blood from an awake child solely for the purpose of the investigation. Thus only children having two halothane anaesthetics within 28 days and who would be anaesthetized again within 28 days were considered suitable for study. When possible, blood was taken at the initial anaesthetic and at each subsequent anaesthetic to permit biochemical assessment of liver function.

After the child was anaesthetized, but before surgery commenced, 1–2 ml of blood was withdrawn from the venous cannula and placed in a

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H. WARK, F.F.A.R.C.S.; M. O'HALLORAN, B.SC., F.A.A.C.B.; J. OVERTON, F.F.A.R.C.S., F.F.A.R.A.C.S.; Royal Alexandra Hospital for Children, Pyrmont Bridge Road, Camperdown, Sydney, Australia.

TABLE I. *Normal laboratory values of liver function tests used*

Liver function test	Normal range	SD
Aspartate amino transferase (AST) ($u\ litre^{-1}$)		
< 1 month	0–105	11
> 1 month	10–40	
Alanine amino transferase (ALT) ($u.\ litre^{-1}$)		
< 1 month	0–90	10
> 1 month	10–50	
Gamma glutamyl transpeptidase (GGT) ($u.\ litre^{-1}$)		
All ages	0–45	3
Alkaline phosphatase (SAP) ($u\ litre^{-1}$)		
< 6 months	60–320	11
6 months–15 yr	4–300	
Adult	15–125	
Bilirubin (TSB) ($mmol\ litre^{-1}$)	3.5–20	0.5

lithium-heparin container. A separate venepuncture was not performed if blood could not be aspirated from the venous cannula inserted by the anaesthetist. Blood taken at the third anaesthetic was used to assess the effect of the first and second anaesthetics on the concentrations of the liver enzymes. If a patient was anaesthetized a fourth time within 28 days of the third halothane anaesthetic, blood was taken again. This blood was used to assess the effect of the second and third anaesthetics on liver function and these results were included in the study as a separate entry. Some children already admitted to the study, presented again for further surgery after a period of months or years. If the entry criteria were again met, these patients were included in the study as a separate entry. The study was approved by the Hospital Ethics Committee.

Laboratory tests

Tests of liver function were performed in the hospital biochemistry department by a biochemist (M. O'H.) who had no knowledge of the patient's anaesthetic history. Serum bilirubin concentration was determined using the method of Jendrassick and Grof (1938). Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ACT), gamma glutamyl transferase (GGT) and alkaline phosphatase (SAP) were determined using an IL Multistat I11 auto analyser. The concentrations of the liver enzymes were measured at 37 °C and the results reported in $u.\ litre^{-1}$. The criterion for an "abnormal" increase in enzyme concentration was that the value after anaesthesia exceeded the preoperative value by more than three standard deviations of the method of analysis. The standard deviation of the method of analysis was calculated from the coefficient of variation of several hundred repeated estimations on "control" sera over the period of the study and is expressed at the upper limit of the "normal" range. The "normal" enzyme ranges and corresponding standard deviations are shown in table I.

RESULTS

Multiple halothane anaesthetics in 1 year

In the 4 years January 1981 to December 1984, 186 patients received 1362 halothane anaesthetics (table II). There were 103 boys and 83 girls. No patient developed clinical signs of liver disease.

Twenty-five patients were anaesthetized with halothane at least 10 times a year. One 5-yr-old boy with an oesophageal stricture caused by the ingestion of a caustic material had 26 halothane anaesthetics in a 12-month period. Another patient with laryngeal papillomata had 42 halothane anaesthetics in 4 years.

Effect of repeated halothane anaesthesia within 28 days on tests of liver function

One hundred and two patients were admitted to this section of the study. Forty-nine patient entries involving 33 patients were excluded from analysis because insufficient blood samples had

TABLE II. *Clinical details of 186 children who had multiple halothane anaesthetics in 1 year. Twenty-three patients were studied for 2 years; four patients were studied for 3 years and three patients were studied for 4 years*

Operation	No. patient entries	No. anaesthetics in 1 year						
		1	2	3	4	5	6	> 6
Neurosurgical	11			2	3	4		2
Airway endoscopy	115		1	8	16	15	17	58
Oesophageal dilatation	9					2		7
Orthopaedic	57		2	28	11	12	2	2
Plastic	10				2	1	2	5
General	21			2	5	7		7
Miscellaneous	3			1				2
Totals	226		3	41	37	41	21	83

TABLE III. *Operations performed in children having a second halothane anaesthetic within 28 days*

Operation	No. patients	No. patient entries
Neurosurgical	5	8
Airway endoscopy	27	69
Oesophageal dilatation	7	33
Orthopaedic	18	21
Plastic	5	10
General	4	5
Miscellaneous	3	3
Totals	69	149

been obtained. There were three reasons for this failure to obtain specimens. First, a patient may not have had the number of repeated halothane anaesthetics that was anticipated. Second, the interval between repeated anaesthetics may not have been sufficiently short. Third, it may not have been possible to withdraw blood from the venous cannula inserted for anaesthetic purposes. Three hundred and ninety-four blood samples were examined. The mean age and standard deviation of children studied was 45.2±46 months with an age range from 2 months to 16 yr.

Operations performed in patients having a second halothane anaesthetic within 28 days are shown in table III. The two major groups of patients were those having repeat laryngoscopy/bronchoscopy for the assessment of airway obstruction and those having peripheral limb surgery, for example bilateral club foot correction.

Changes in liver function tests in patients receiving two halothane anaesthetics within 28 days are shown in table IV. The average age of children in whom there was an abnormal increase in serum AST and ALT concentrations was 47±35 months and 41±24 months, respectively. The highest postoperative serum transaminase concentrations were an AST of 171 u. litre^{-1} and an ALT of 198 u. litre^{-1}. Both patients had two neuroradiological procedures within 14 days for the investigation of an intracranial mass.

Children older than 5 yr did not develop increases in liver enzyme concentrations more frequently than younger children. The 10 children in the study older than 12 years of age did not show any evidence of abnormal increases in enzyme concentrations.

The responses to the halothane anaesthesia, of children in whom the preoperative enzyme concentrations were increased, are shown in table V. Five children had an increase in serum AST concentration and two an increase in serum ALT concentration on initial entry to the study.

TABLE IV. *Changes in liver function tests after two halothane anaesthetics within 28 days. †Days, following second anaesthetic, that liver function tests were performed*

Days of tests†	No. patient entries	No. patient entries with increased values after testing: AST	ALT	GGT	SAP	TSB
0–7	49	5	3	1	1	0
7–14	31	2	1	1	1	0
14–28	69	9	3	2	2	0
Totals	149	16(10.6%)	7(4.7%)	4(2.6%)	4(2.6%)	0

TABLE V. *Responses to halothane in children with preoperative increases in liver enzyme concentrations. Liver function tests were measured within 1 month of the second halothane anaesthetic*

Liver function tests	No. patient entries	Change in concentration: Increase	Decrease	No change
AST	21	2	4	15
ALT	9	1	5	3
GGT	4	1	0	3
SAP	1	0	1	0

DISCUSSION

Adult patients having multiple halothane anaesthetics at short intervals (4–8 weeks) are at particular risk of developing halothane-associated hepatitis (Inman and Mushin, 1978).

In our prospective study in children over the 4-year period January 1981 to December 1984, 186 patients had 1362 halothane anaesthetics. No patient developed clinical evidence of liver disease, although minor hepatic dysfunction may have been missed. Likewise, Kennedy, Chinyanga and Steward (1981) in a 12-year retrospective review of 1922 halothane anaesthetics in 285 children having laryngeal surgery at the Hospital for Sick Children, Toronto, found no evidence of postoperative jaundice.

Two prospective studies in children have looked at alterations in the concentrations of the liver enzymes following a single halothane anaesthetic. Lomaz (1965) reported a series of 20 children in whom AST and ALT values were determined at the beginning and at the end of halothane anaesthesia. Resurrection and colleagues (1980), using a similar method, collected data on eight children. No changes in liver enzymes were detected in either of these studies. However, the interval between exposure to halothane and onset of hepatitis can be as long as 28 days. Normal liver enzyme values in the immediate postoperative period cannot be interpreted as excluding halothane-induced liver dysfunction.

Our study in children examined the effect on liver function of two halothane anaesthetics within 28 days. Sixty-nine patients were studied on 149 occasions. No patient became jaundiced and there were no sequelae related to anaesthesia. Postoperative AST concentrations were increased on 16 occasions (10.6%). In adults, Wright and co-workers (1975) found a 20% incidence of increased AST concentrations following repeat halothane at short intervals.

Increases in postoperative ALT concentration were noted on seven occasions (4.7%)—an incidence substantially less than that reported in adults by Trowell, Peto and Crampton-Smith (1975). These authors found that four of 18 patients (22%) given repeat halothane anaesthetics at short intervals developed ALT concentrations greater than 100 u. litre^{-1}.

Dundee and colleagues (1981) found that 50% of adult patients having an interval of 1–6 weeks between halothane anaesthetics had an abnormal increase in GGT concentration. In our series only 2.7% of children developed abnormalities of GGT after two halothane anaesthetics within 28 days.

Some children in the study had minor abnormalities of liver enzyme(s) in blood taken before the halothane anaesthetic. This was usually a result of the hepatitic effects of a systemic viral illness. Many of the children in the study had either viral croup or a lower respiratory tract infection secondary to upper airway obstruction. The response of these patients to a further halothane anaesthetic within 28 days was variable, but in the majority of patients the concentrations of the liver enzyme(s) either remained unchanged or decreased. This finding supports the work of Dundee and colleagues (1981), who found that adults with slight increases in enzyme concentration before halothane anaesthesia were not more likely than other subjects to develop further changes.

Transaminase concentrations of greater than 1000 u. litre^{-1} are associated with severe hepatitis and values less than 150 u. litre^{-1} with mild disease, but correlation with liver necrosis in the individual patient is poor (Rosali, 1976). In our series, two patients developed serum transaminase values greater than 150 u. litre^{-1}: one patient had an AST of 171 u. litre^{-1} and another an ALT of 198 u. litre^{-1}. Neither had any other evidence of liver disease while in hospital, or after discharge.

Minor changes in liver function are common in the period immediately after operation and may be the result of surgical trauma, hypoxia, hypotension and anaesthetic agents (Nickell and Allbritten, 1957; Person and Judge, 1958; Clark, Doggart and Lavery, 1976). Our study in children showed that the incidence of minor disturbances in serum transaminase values following repeated halothane anaesthesia within 28 days was 5% and 11%.

Fatal postoperative hepatic failure following halothane in children is rare. Less than 20 cases have been reported in the world literature since the introduction of halothane to clinical practice in 1957. Our study supports the view of Strunin (1979) that minor abnormalities of liver enzymes and fulminant hepatic failure following halothane are two separate, unrelated entities.

Several authors (Inman and Mushin, 1978; Sherlock, 1978; Neuberger and Williams, 1984) recommend that patients who are likely to require multiple anaesthetics within a short period should not be given halothane more than once. We feel that in children, this restriction on the use of halothane is unwarranted.

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HISTAMINE RELEASE DURING THE ADMINISTRATION OF ATRACURIUM OR VECURONIUM IN CHILDREN

N. G. GOUDSOUZIAN, E. T. YOUNG, J. MOSS AND L. M. P. LIU

SUMMARY

The histamine releasing potential of equivalent bolus doses of atracurium 0.6 mg kg^{-1} or vecuronium 0.12 mg kg^{-1} was evaluated in 20 children anaesthetized with halothane. Blood samples were obtained before, and at 2 and 5 min after the administration of the neuromuscular blocker. The twitch response to 0.15 Hz was also evaluated. None of the 10 patients receiving vecuronium had a significant increase in plasma histamine concentration. In two of the 10 children receiving atracurium, the plasma histamine concentration increased markedly, but without any apparent clinical manifestations. Recovery of neuromuscular function (to 95% twitch height) after vecuronium 0.12 mg kg^{-1} was faster than after atracurium 0.6 mg kg^{-1} ($P < 0.02$).

Release of histamine is one of the side effects associated with the administration of non-depolarizing neuromuscular blocking drugs. It is seen frequently with tubocurarine, less with metocurine and rarely with atracurium (Basta et al., 1983); pancuronium and vecuronium seem to be free of histaminergic properties. Clinical manifestations of histamine release (confirmed by the measurement of plasma histamine concentration (Scott et al., 1985)) include a skin rash and, occasionally, mild systemic arterial hypotension (Mirakhur et al., 1983; Rowlands 1983). With the refinement of the plasma histamine assay at a sensitivity in the range of pg ml^{-1}, more sensitive evaluations can be performed.

There is a general feeling among paediatric anaesthetists that children differ from adults in regard to the side effects commonly associated with the release of histamine. Hypotension, for instance, seems to be rare in children, and skin rashes, although observed occasionally in adolescents (Goudsouzian, Liu and Savarese, 1978; Goudsouzian et al., 1983), are infrequent in the young, especially in those younger than 10 years of age. In fact, most of the observed histaminomimetic reactions in children have been observed locally along the tract of the injected vein (Nightingale and Bush, 1973, 1983). It is unknown whether this difference is attributable to a lesser release of histamine than in the adult, or whether the child's end organs are simply less responsive.

The recent introduction of atracurium and vecuronium to clinical practice has led to a close evaluation of their side effects. While the implications of histamine release have been well defined in adults (Scott et al., 1985), no study in children has yet addressed this problem.

PATIENTS AND METHODS

Twenty healthy children (ASA I) aged 1–10 yr were studied. The design of the study was approved by the Subcommittee on Human Studies, Committee on Research, of the Massachusetts General Hospital, and written parental consent was obtained.

Premedication in children younger than 7 yr consisted of methohexitone 25 mg kg^{-1} per rectum; older children were not premedicated. Anaesthesia was induced with nitrous oxide and halothane in oxygen via a face mask, the inspired halothane concentration being maintained at 1–1.5%. Heart rate, arterial pressure (by auscult-

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N. G. GOUDSOUZIAN, M.D.; E. T. YOUNG, M.D.; J. MOSS*, M.D.; L. M. P. LIU, M.D.; Department of Anaesthesia, Harvard Medical School at Massachusetts General Hospital, Boston, MA 02114, U.S.A.

* Present address: Department of Anesthesia and Critical Care, University of Chicago, Chicago, Il, U.S.A.

Reprint requests to N. G.

TABLE I. *Age and weight of the patients and cardiovascular variables before and after the administration of atracurium or vecuronium (mean values ± SEM)*

			Systolic arterial pressure			Heart rate		
Drug	Age (yr)	Weight (kg)	Before (mm Hg)	After (mm Hg)	Change (%)	Before (beat min^{-1})	After (beat min^{-1})	Change (%)
Atracurium	4.6±0.9	19.3±2.4	87.4±5.5	85.3±5.2	−3.3±1.9	102.6±8.9	105.1±8.9	5.8±2.7
Vecuronium	5.4±0.8	21.1±1.9	88.8±3.2	92.3±3.7	4.3±1.8	96.0±6.0	98.2±7.2	1.6±4.8

TABLE II. *Histamine concentrations (mean ± SEM and range) before and after the administration of atracurium and vecuronium in children*

	Histamine concn (pg ml^{-1})		
	Control	2 min	5 min
Atracurium 0.6 mg kg^{-1}	794±126	1780±56	981±255
	424–1834	411–10250	471–2755
Vecuronium 0.12 mg kg^{-1}	567±62	570±105	557±91
	148–832	110–1187	185–1302

ation), the electrocardiogram, and temperature were monitored. The end-expired carbon dioxide concentration was maintained at 4.6–6 kPa (35–45 mm Hg).

Neuromuscular transmission was evaluated by recording the force of contraction of the adductor pollicis in response to indirect stimulation of the ulnar nerve at the wrist via surface electrodes; supramaximal single twitch stimuli at a rate of 0.15 Hz were used. The force of contraction was transduced by a Grass force displacement (FT-03) transducer and was recorded on a Grass polygraph.

Once the children were anaesthetized, a blood sample (control) was obtained. A bolus dose of atracurium 0.6 mg kg^{-1} or vecuronium 0.12 mg kg^{-1} was administered randomly to provide two study groups of 10 patients each. Two and 5 min after the administration of the myoneural blocker, additional blood samples were taken. Tracheal intubation was performed after the second (2-min) sample was withdrawn.

The blood samples were collected in dry heparinized syringes, transferred to plastic tubes, and placed immediately on ice. Cold centrifugation was performed soon thereafter, and the plasma separated and frozen.

The plasma samples were analysed by radio-enzymatic assay. This technique is sensitive to 25 pg ml^{-1} (Beavan, Jacobsen and Horakova, 1972; Verburg, Bowsher and Henry, 1983). The inter- and intra-assay variations were 8% in our laboratory. The samples were assayed in duplicate with duplicate internal standards.

Statistical analysis was performed by non-correlated Student's t test. Data were considered significant at $P < 0.05$.

RESULTS

The children studied were aged 1–10 yr and their weights varied between 9 and 32 kg. There were no significant differences in the ages and the weights of the two groups of patients studied (table I), nor were there significant differences in the cardiovascular variables before and after the administration of the neuromuscular blocking drug (table I).

The mean control plasma histamine concentration from all the children studied during halothane anaesthesia was 681±73 pg ml^{-1} (mean ± SEM). The changes following the administration of the neuromuscular blocker were not significant in either group (table II). The response of two patients in the atracurium group was, nevertheless, quite striking. The first was a child with a high control plasma histamine concentration (1834 pg ml^{-1}) which increased to 10250 pg ml^{-1} 2 min after the administration of atracurium before decreasing subsequently to near her control

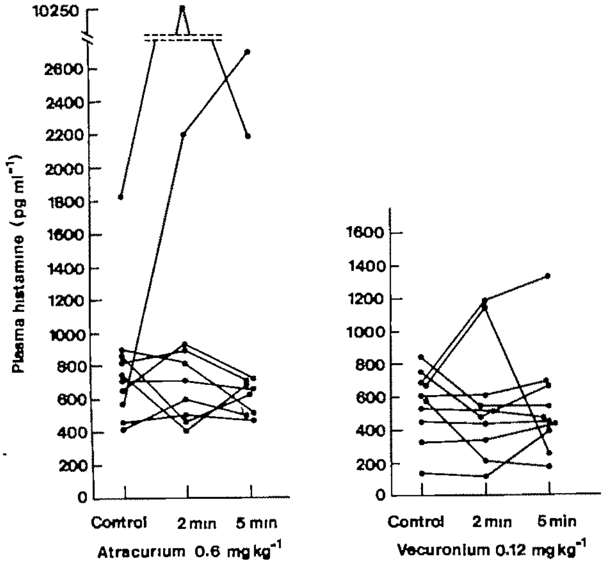

FIG. 1. Individual changes in plasma histamine concentration after the administration of atracurium 0.6 mg kg^{-1} and vecuronium 0.12 mg kg^{-1} in children.

values within 5 min (fig. 1). Her systolic arterial pressure decreased slightly from 80 mm Hg to 70 mm Hg with no change in heart rate. She did not develop any rash. Retrospectively, close inquiry of the mother revealed that this child had frequent symptoms of rhinorrhea. However, she did not need any special treatment and was not receiving any medication. She did not have any other allergic symptoms.

In the second, a 7-yr-old boy whose histamine concentration was within the normal control range (567 pg ml^{-1}), the histamine concentration quadrupled after atracurium, and remained increased at 2755 μg ml^{-1} for at least 5 min. There were no haemodynamic changes. In the remaining eight patients there was little change in the plasma histamine concentrations (control 693 ± 60; 2 min 668 ± 75; 5 min 606 ± 41 pg ml^{-1}).

In the vecuronium group, two patients also merited some attention. In the first the plasma histamine concentration increased from 685 to 1187 pg ml^{-1} at 2 min, and then to 1302 pg ml^{-1} at 5 min. In the second, the concentration increased by the same magnitude at 2 min but had returned to the control value at 5 min (fig. 1). These changes were less pronounced than those in the atracurium patients and were not accompanied by changes in heart rate or arterial pressure. None of the patients in either group developed a skin rash.

The onset of action of the equipotent doses of the two drugs was comparable: 1.9 min for atracurium, 2.2 min for vecuronium (table III). Although the recovery index (25–75 % recovery) was comparable in the two groups, time to full recovery was somewhat longer in the atracurium group. The recovery of the twitch to 5 % and from 5 % to 25 % was significantly longer ($P < 0.001$ and $P < 0.05$) after atracurium than after vecuronium and, hence, the total recovery time to 95 % twitch height was also significantly longer ($P < 0.02$).

DISCUSSION

Histamine

One important observation of this study was the infrequent increase in plasma histamine concentration in the atracurium group, a result different from that obtained in studies in adults conducted similarly. For example, Scott and colleagues (1985) studied a group of nine adults who also received a bolus of atracurium 0.6 mg kg^{-1}. Plasma histamine concentrations were measured using the same technique. The mean control value was 715 ± 94 pg ml^{-1}, a value comparable to that obtained in the children. However, after this dose the plasma histamine concentration increased, on average, in most of the adults, to about twice the control value, the mean concentration being 1415 ± 203 pg ml^{-1} before decreasing to

Table III. *Times (min) (mean ± SEM) to onset of the maximum twitch depression (D_{max}) and the recovery of the twitch response (min)*

Drug	Inject. to D_{max}	Recovery of twitch height				
		D_{max}–5 %	5–25 %	25–75 %	5–95 %	Total
Atracurium 0.6 mg kg^{-1}	1.9 ± 0.2	38.8 ± 2.7	9.7 ± 1.5	11 ± 1.6	24.3 ± 3.0	58.7 ± 4.2
Vecuronium 0.12 mg kg^{-1}	2.2 ± 0.3	21.4 ± 1.2	5.8 ± 0.6	10.5 ± 1.2	22.9 ± 2.5	44.6 ± 2.7
P		< 0.001	< 0.05			< 0.02

1086 ± 238 pg ml^{-1} at 5 min. In our sample of 10 children, the change in the mean plasma histamine concentration was similar in direction, but insignificant statistically. More important, however, were the changes in certain individuals. Most of the adults showed moderate changes in plasma histamine concentration, each contributing to the mean increase. In contrast, the mean change in the children was attributable to results in two patients: the one with a high control value had a five-fold increase at 2 min which returned to control within 5 min (fig. 1). To exclude the possibility of laboratory error, this patient's samples were re-assessed against known controls and the results found to be accurate. Interestingly, the measured increase in histamine concentration in this subject was comparable to that previously reported in a child who had a cutaneous reaction, bronchospasm, and hypotension following the rectal administration of methohexitone. That child's plasma histamine concentration was 6270 pg ml^{-1} after ephedrine and diphenhydramine (Liu, Liu and Moss, 1984).

In further contrast to the findings in the adult studies was the fact that, in our sample, both clinical and cardiovascular changes were minimal, even when the plasma histamine concentrations were increased. Again, in the child with the five-fold increase in plasma histamine concentration, systolic arterial pressure decreased by only 10 mm Hg. We did not measure arterial pressure directly in this patient, or in any of the others, because we could not justify the insertion of an intra-arterial cannula in healthy children; we could easily, however, have detected significant cardiovascular changes with the precordial stethoscope, minute by minute auscultation of arterial pressure, and by electrocardiography with a digital readout.

These data confirm our clinical impression that histamine release after atracurium is less of a problem in children than in adults. In our earlier clinical studies with atracurium 0.4 mg kg^{-1}, no rashes were detected in children; mild rashes have, however, been seen in adolescents (Goudsouzian et al., 1983). An isolated case of generalized rash with minimal hypotension and, possibly, bronchospasm in an 11-yr-old boy has been reported (Aldrete, 1985). Furthermore, when atracurium is given following thiopentone in a small vein at a dose of 0.6 mg kg^{-1} a local histamine-like response or reddening of the vein proximal to the injection site has been noted. This effect is more pronounced in adolescents than in children 5–10 yr, and is seen least of all in children younger than 5 yr (Nightingale and Bush, 1983).

There are no data in the literature on the incidence of histamine release (*in vivo*) after the administration of other drugs in children. It is our impression that this is the first study of this problem. Marone and coworkers (1983) have, however, addressed the effect of age with respect to histamine release from basophils *in vitro*. They found that, with increasing age, more histamine was released at any concentration of anti-IgE. They also found an increase with age in the maximum percent histamine release induced by an optimal anti-IgE concentration. In their study the youngest children (0–9 yr) exhibited the least response, with the older age group (up to 60 yr) showing a progressively greater increase. In our study of children 1–10 yr we did not find any special tendency; neither the control histamine concentration nor the percent increase was related to specific age.

Pharmacodynamics

The times to onset of action (interval to maximum depression of the twitch) of atracurium and vecuronium were comparable—approximately 2 min. At the equipotent doses of 0.6 mg kg^{-1} and 0.12 mg kg^{-1}, respectively, these drugs provided excellent conditions for intubation at approximately 2.5 min after administration. The duration of complete paralysis (absent twitch response) proved longer ($P < 0.001$) with atracurium (38.8 ± 2.7 min) than with vecuronium (21.4 ± 1.2 min), indicating that a single dose of vecuronium will generally be shorter-acting than atracurium. Hence, at these doses vecuronium is probably a better choice for relatively short procedures. It remains true, however, that the recovery index was comparable for the two drugs, and that once recovery had started the rates of recovery were practically the same.

In a previous study conducted in the same manner with a similar rate of frequency of stimulation, we found that a dose of atracurium 0.4 mg kg^{-1} produced maximum twitch depression in 3.7 ± 0.4 min, with the duration of complete paralysis lasting 19.4 ± 1.6 min (Goudsouzian et al., 1986). In the present study the larger dose (0.6 mg kg^{-1}) markedly improved the onset time (1.9 ± 0.2 min), but increased the duration of complete paralysis to 38.8 ± 2.7 min. With the larger dose, conditions for intubation were rated excellent in all patients. When evaluated after 0.4 mg kg^{-1}, conditions were considered excellent in only 80% of the cases (Goudsouzian et al., 1983).

CONCLUSION

It remains difficult to ascertain whether the release of histamine is of concern in children. Neither of the two children cited above in whom the concentration of histamine increased following atracurium showed any significant cardiovascular changes or clinical signs such as a rash. However, we may conclude that, as a general rule, a large bolus dose of atracurium should best be avoided in an asthmatic patient, since such a dose may possibly trigger an attack. Vecuronium may be a better choice. If atracurium is for some reason indicated, it may be safely administered at a slow rate, as this technique has been shown to decrease markedly histamine release in adults (Scott et al., 1985). For short procedures where suxamethonium has to be avoided, vecuronium might be a better choice than atracurium on account of its shorter duration of action.

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VENTILATION, VENTILATORY CARBON DIOXIDE AND HORMONAL RESPONSE DURING HALOTHANE ANAESTHESIA AND SURGERY IN CHILDREN AFTER MIDAZOLAM PREMEDICATION

A. J. CHARLTON, D. J. HATCH, S. G. E. LINDAHL, J. M. PHYTHYON AND N. E. NORDÉN

SUMMARY

In 14 intubated, spontaneously breathing children with body weight (bw) ranging from 8.3 to 25.6 kg, the influence of midazolam 0.1 mg kg⁻¹ i.m. (group $M_{0.1}$*, n = 7) and 0.2 mg kg⁻¹ i.m. (group* $M_{0.2}$*, n = 7) as premedication, on sedation, ventilation, ventilatory response to carbon dioxide and hormonal stress response was studied in connection with minor surgical procedures during halothane anaesthesia. The concentrations of catecholamines, ACTH and cortisol were measured immediately after induction, during undisturbed anaesthesia, during surgery and 15 min after the end of the surgical procedure. Sedation was better and plasma catecholamine concentrations during undisturbed anaesthesia were less in children receiving the larger dose of midazolam. During surgery and in recovery there were no differences in hormone concentrations. In recovery, the concentrations of all hormones were significantly greater compared with during undisturbed anaesthesia. During surgery,* $\dot{V}_E$ *and respiratory rate were somewhat lower in group* $M_{0.2}$ *while* E'_{CO_2} *was similar. A dose dependent depression of the response to carbon dioxide was found. However, clinically, the ventilatory response to carbon dioxide after surgery was considered to be adequate in both groups.*

Although diazepam has suitable anxiolytic and amnesic properties, its use as a premedicant has been limited by local irritation when given i.m. (Siebke, Ellertsen and Lind, 1976), and its unpredictable bioavailability (Morselli et al., 1973; Dundee, Gamble and Assaf, 1974; Korttila and Linnoila, 1975). Midazolam, which is water soluble, has almost no local irritating effect (Cole, 1982; Vinik, Reves and Wright, 1982) and is absorbed rapidly after i.m. administration (Crevoisier et al., 1981). It has potent anxiolytic (Dundee et al., 1980) and amnesic effects (Dundee and Wilson, 1980) and has been used i.m. in adults as a premedicant in doses of 0.07 and 0.08 mg kg^{-1} (Vinik, Reves and Wright, 1982; Fragan et al., 1983).

In the present study the influence of two doses of midazolam (0.1 and 0.2 mg kg^{-1}) i.m. for premedication, on ventilation, ventilatory response to carbon dioxide and hormonal responses were investigated in spontaneously breathing children during halothane anaesthesia.

PATIENTS AND METHODS

Anaesthetic technique

Fourteen children (ASA class I) were studied in groups premedicated with atropine 0.02 mg kg^{-1}

A. J. CHARLTON*, M.B., CH.B., F.F.A.R.C.S.; D. J. HATCH, M.B., B.S., F.F.A.R.C.S.; S. G. E. LINDAHL†, M.D., PH.D.; N. E. NORDÉN‡, M.D., PH.D; J. M. PHYTHYON§, M.D.; Department of Anaesthesia, The Hospital for Sick Children, Great Ormond Street, London.

Present addresses:

*Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

†Department of Anaesthesia; ‡Department of Clinical Chemistry, University Hospital, S-221 85 Lund, Sweden.

§Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee 37232, U.S.A.

TABLE I. *Mean values (±1 SD) for body weight, premedication time and duration of operation are presented in the two groups.* *Year, months, weeks

Patient no.	Age*	Body weight (kg)	Diagnosis	Premed. time (min)	Operation time (min)
Midazolam 0.1 mg kg^{-1} + atropine 0.02 mg kg^{-1}					
1	3, 8, 0	16.9	Squint	40	35
2	3, 5, 0	15.0	Extirp. of neck lymph node	61	13
3	6, 2, 0	25.6	Extirp. of thyroglossal cyst	80	61
4	6, 0, 0	22.5	Undescended testicle	70	35
5	2, 11, 1	13.0	Squint	100	65
6	7, 8, 0	19.5	Exploration left groin	75	45
7	4, 9, 0	18.0	Undescended testicle	88	80
Mean ± 1SD		18.5 ± 4.1		73.4 ± 17.9	47.7 ± 20.9
Midazolam 0.2 mg kg^{-1} + atropine 0.02 mg kg^{-1}					
1	8, 4, 3	20.0	Excision of submand. gland.	75	55
2	2, 7, 1	16.3	Inguinal hernia	45	120
3	8, 5, 2	23.6	Symphyseal web	50	102
4	1, 5, 0	8.3	Extirp. of neck lymph node	75	65
5	4, 8, 0	15.0	Osteoid osteoma left leg	70	85
6	8, 4, 2	25.0	Squint	40	55
7	7, 8, 2	24.2	Retinoblastoma	50	55
Mean ± 1SD		18.9 ± 5.6		57.9 ± 13.9	76.7 ± 24.3

and either midazolam 0.1 mg kg^{-1} (group $M_{0.1}$) or midazolam 0.2 mg kg^{-1} i.m. (group $M_{0.2}$). Minute ventilation ($\dot{V}$E), tidal volume (VT), respiratory frequency (f) and end-tidal carbon dioxide concentration (E'_{CO_2}) were measured before and during surgery and immediately after surgery with and without the inhalation of carbon dioxide. Blood for analysis of hormone concentrations was drawn after the induction of anaesthesia, during surgery and 15 min after the end of surgery. The study was approved by the Ethics Committee at the hospital. Characteristics of the patients and details of the surgical procedures are presented in table I.

After the induction of anaesthesia with cyclopropane in oxygen ($F\text{I}_{O_2}$ 0.5), suxamethonium 1–1.5 mg kg^{-1} was used to facilitate intubation. The patients were then allowed to resume spontaneous breathing with nitrous oxide in oxygen ($F\text{I}_{O_2}$ 0.5), and 0.5–2.0% halothane. A modified T-piece (Mapleson F system) (fig. 1) was used and fresh gas flows were adjusted to prevent rebreathing. Arterial pressure and heart rate were measured automatically (Dinamap 850: Applied Medical Research, Tampa, Florida, U.S.A.). The paediatric airway adaptor of an in-line capnograph (Hewlett–Packard 14360 A) and a heated pneumotachograph (Fleisch No. 0) with a differential pressure manometer (Validyne MP 45-1-871, range ± 2 cm H_2O) were placed in the patient limb of the T-piece for measurements of E'_{CO_2} and $\dot{V}$E (fig. 1). VT was measured by

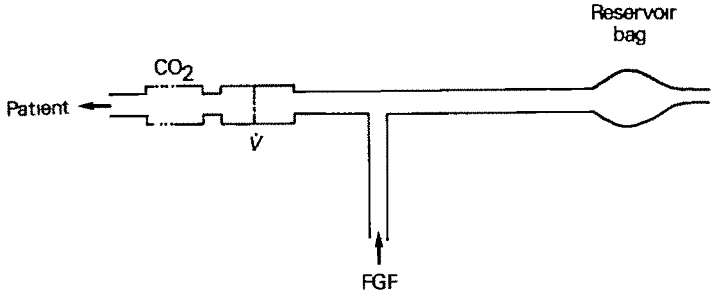

FIG. 1. Schematic presentation of the breathing system. CO_2 = position of in-line capnograph; $\dot{V}$ = position of pneumotachograph; FGF = fresh gas flow inlet.

electrical integration of the flow signal. Flow, volume and carbon dioxide signals were recorded on a u.v. recorder (S.E. Labs (EMI) Ltd, S.E. 3006). Certified gases were used to calibrate the capnograph and a 50-ml syringe containing 50% nitrous oxide in oxygen mixture to calibrate the volume.

The resistance of the system was 10.0 cm H_2O litre^{-1} s^{-1} up to flow rates of 10 litre min^{-1} and its deadspace was 6 ml (measured by water displacement).

Biochemistry

Samples for the analysis of ACTH and cortisol concentrations were collected in test tubes containing EDTA 10.0 mg/7 ml blood and aprotinin (Trasylol, Bayer, Wester Germany) 300 KIE/7 ml blood which had been prechilled in ice-water. The samples were kept at 0 °C until centrifugation in a refrigerated centrifuge. The plasma was then stored at −70 °C. ACTH was determined by radioimmunoassay (ACTHK, Sorin Biomedica, Italy) using rabbit antiserum raised against porcine ACTH coupled to bovine serum albumin. Human ACTH was used as standard and ^{125}I-ACTH as tracer (Hedner, Nordén and Valdemarsson, 1981). The concentration of cortisol was determined using solid phase radioimmunoassay (Gammacoat, Clinical Assays, Mass. U.S.A.) with rabbit anti-cortisol serum attached to test tubes as binding protein and ^{125}I-cortisol as tracer. Samples to permit measurement of the total catecholamine concentration were drawn in tubes with 20 µl of anticoagulant and anti-oxidant (EGTA 90 mg ml^{-1}, glutathione 60 mg ml^{-1} and pH 6.0–7.4) per ml of blood. A modification of the radioenzymatic method of Passon and Peuler (1973) (Upjohn Diagnosis, U.S.A.) based on rat liver catechol-O-methyltransferase and S-adenosyl-L-methionine-(^{3}H-methyl) was used. After periodate oxidation, the resulting ^{3}H-vanillin was extracted and measured by liquid scintillation. Between-runs coefficient of variation for the assay is 4–10% depending on concentration. Normal values for adults are 0.8–2.4 nmol litre^{-1}.

Measurements

The sedative effect of the premedication was evaluated, according to the scoring system given in table II, by the anaesthetist in charge of the patient. He was not involved in the study and did not know the premedication used. Because of diurnal variations in the hormone concentrations, blood samples were drawn between 10 a.m. and 2 p.m. Immediately after induction and during undisturbed anaesthesia before tracheal intubation (UA), blood was drawn from a peripheral vein. The second blood sample was drawn during surgery (DS) and the third, 15 min (P) into the postoperative period.

Table II. *Evaluation of premedication*

	Score
Behaviour of the child	
Crying	1
Anxious	2
Calm	3
Asleep	4
Reaction to induction of anaesthesia	
Unco-operative	1
Slight resistance	2
Co-operative	3
None	4

At least 20 min after the induction of anaesthesia but before the start of surgery (PS), $\dot{V}$E, VT, f, E'_{CO_2}, arterial pressure and heart rate were measured, and repeated at a stable state during surgery (DS) and immediately after surgery during continued anaesthesia before extubation, with and without the addition of about 2% carbon dioxide to the inspired gas.

Statistics

Mean values, standard deviation (SD) and standard error of the mean (SEM) were calculated and unpaired Student's t test applied to mean data.

RESULTS

In group $M_{0.1}$, premedication was given 73±18 min (mean±1 SD) and in group $M_{0.2}$, 58±14 min (mean±1 SD) before the induction of anaesthesia (ns) (table I). Evaluation of preoperative sedation resulted in a mean scoring of 4.7 after $M_{0.1}$ and 5.7 after $M_{0.2}$. In the anaesthetic room immediately after induction, respiratory rate and heart rate (mean values±1 SD) were 35±11 b.p.m. and 108±23 beat min^{-1} with the smaller and 32±7 b.p.m. and 109±9 beat min^{-1} with the larger dose of midazolam. E'_{CO_2} (mean±1 SD) was 4.9±0.6% with $M_{0.1}$ and 5.3±0.8% with $M_{0.2}$. None of these differences was statistically significant. At measurements before, during and after surgery with and without carbon dioxide

TABLE III. *Mean values (±1 SD) of systolic arterial pressure (SAP) and heart rate (HR) in the two groups $M_{0\,1}$ and $M_{0\,2}$ before, during and after surgery without and with carbon dioxide breathing*

	Before surgery	During surgery	After surgery	After surgery during CO_2
SAP (mm Hg)				
$M_{0\,1}$	103±7.3	104±4.5	106±4.9	108±7.9
$M_{0\,2}$	98±6.7	100±8.2	101±7.6	103±9.4
HR (beat min^{-1})				
$M_{0\,1}$	112±24	120±24	124±20	127±18
$M_{0\,2}$	112±12	117±12	115±13	119±13

inhalation, systolic arterial pressure and heart rate were similar within each group as well as between the two groups (table III).

Ventilation

In the group of children receiving the smaller dose of midazolam, $\dot{V}$E was greater during surgery because of more rapid respiratory rates. E'_{CO_2} was similar in the two groups (fig. 2). After surgery, E'_{CO_2} was unaltered before and during the inhalation of 2.13±0.22% (mean±1 SD) carbon dioxide in the $M_{0.1}$ group. In group $M_{0.2}$, E'_{CO_2} increased by about 8% (ns) when 2.18±0.29% (mean±1 SD) carbon dioxide was inhaled after surgery. At comparisons before and during the inhalation of carbon dioxide, $\dot{V}$E and VT were both increased to the same extent in the two groups (fig. 3). The relationship between percentage difference in $\dot{V}$E and the change in E'_{CO_2} revealed a somewhat more depressed ventilation in group $M_{0.2}$ compared with that in group $M_{0.1}$ (fig. 4).

Stress response

Plasma catecholamine concentration (mean±1 SD) was 4.40±1.82 nmol $litre^{-1}$ in $M_{0.1}$ during undisturbed anaesthesia after the induction of anaesthesia ($P < 0.05$) (fig. 5). There were no

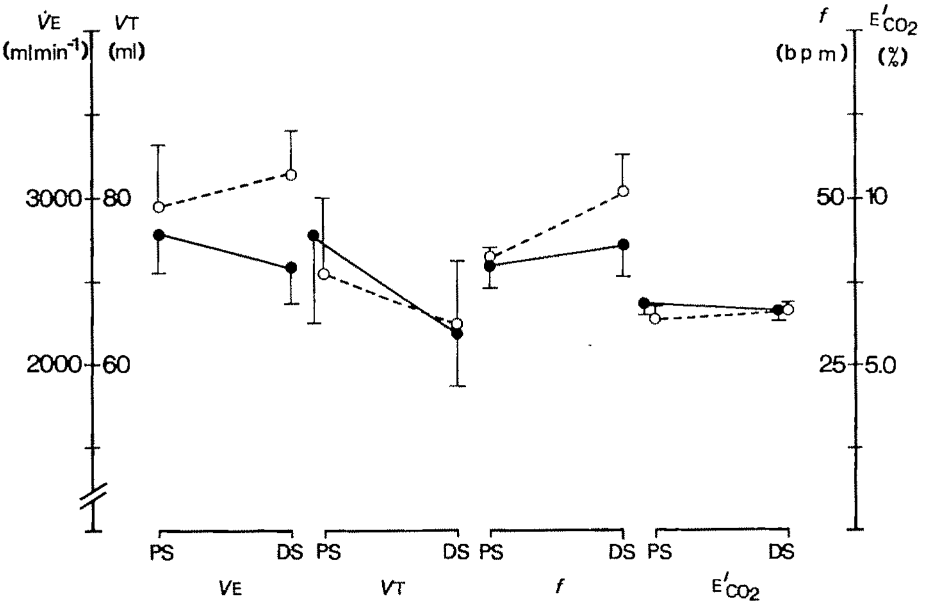

FIG. 2. Mean values±SEM of minute ventilation ($\dot{V}$E), tidal volume (VT), respiratory rate (f) and end-tidal carbon dioxide concentration (E'_{CO_2}) before surgery (PS) and during surgery (DS) after premedication with midazolam 0.1 mg kg^{-1} (○---○) and with midazolam 0.2 mg kg^{-1} (●——●).

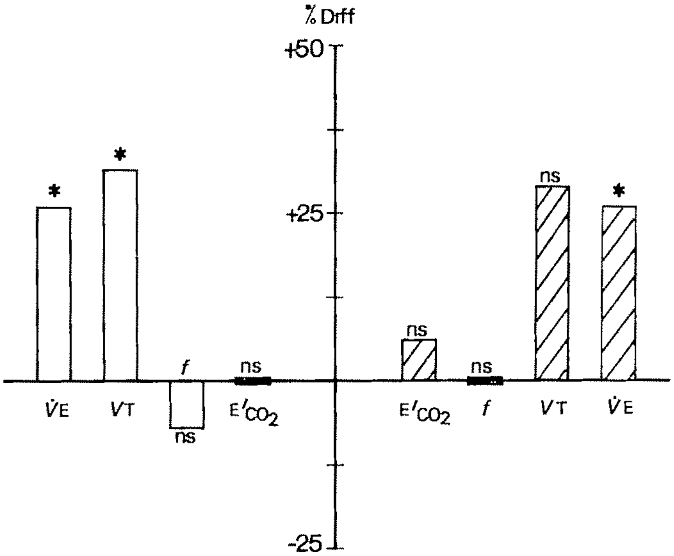

FIG. 3. Percentage change (% Diff.) in mean values of V̇E, VT, f and E'_{CO_2} from before to during inhalation of carbon dioxide (I_{CO_2}), in groups $M_{0.1}$ ($I_{CO_2} = 2.13 \pm 0.22\%$) (open columns) and $M_{0.2}$ ($I_{CO_2} = 2.18 \pm 0.29\%$) (hatched columns) $^*P < 0.05$, ns = not significant.

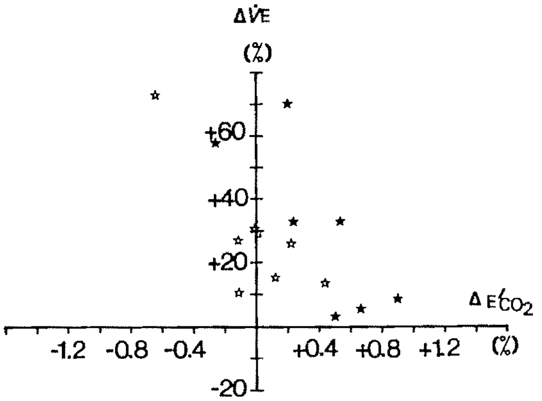

FIG. 4. Relationship between percentage differences in V̇E (ΔV̇E) and absolute changes in end-tidal carbon dioxide concentration ($\Delta E'_{CO_2}$) in group $M_{0.1}$ (open stars) and in group $M_{0.2}$ (filled stars).

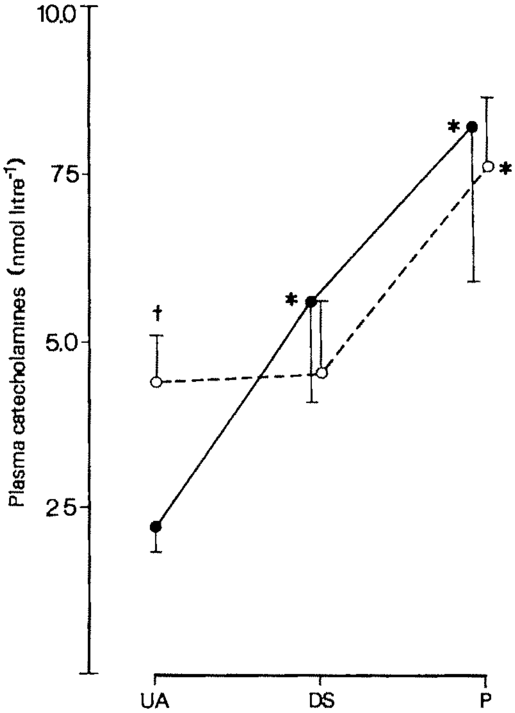

FIG. 5. Mean values (± SEM) of plasma catecholamine concentration after induction (UA) during surgery (DS) and 15 min after operation (P) in group $M_{0.1}$ (○- - -○) and in group $M_{0.2}$ (●——●). $^\dagger P < 0.05$ for the difference at UA between the groups; $^*P < 0.05$ for the differences within each group compared with UA.

differences in plasma catecholamines between the two groups during surgery, and 15 min after the end of the operation.

In group $M_{0.1}$, plasma catecholamine concentration during undisturbed anaesthesia was not further increased during surgery, whereas the mean value during undisturbed anaesthesia in group $M_{0.2}$ was increased by 255% during surgery ($P < 0.05$). In both groups, mean concentrations of the catecholamines were significantly increased 15 min after surgery ($P < 0.05$) (fig. 5). During undisturbed anaesthesia, the mean (±1

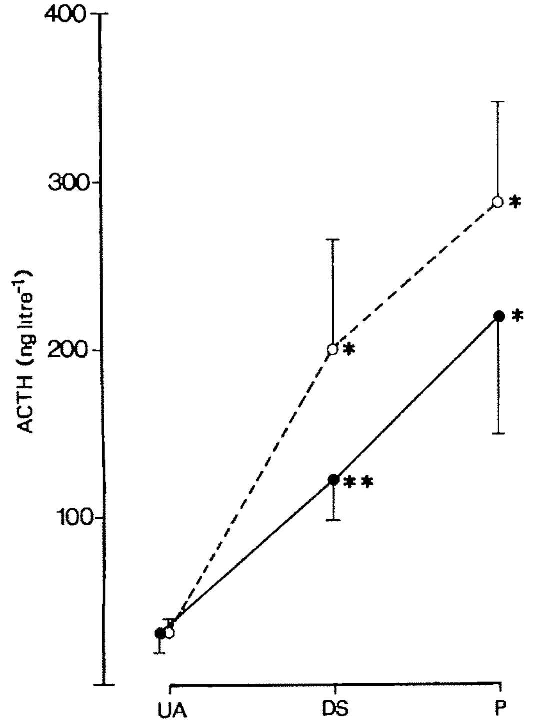

FIG. 6. Mean values (± SEM) of plasma ACTH concentration at UA, DS and P in group $M_{0.1}$ (○---○) and in group $M_{0.2}$ (●——●) $*P < 0.05$; $**P < 0.01$; for the differences within each group compared with UA.

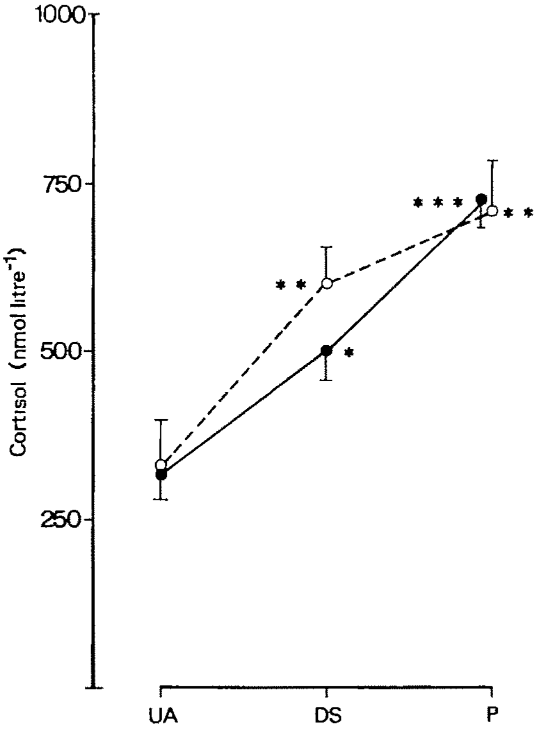

FIG. 7. Mean values (± SEM) of plasma cortisol concentration at UA, DS and P in group $M_{0.1}$ (○---○) and in group $M_{0.2}$ (●——●) $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ for the differences within each group compared with UA.

SD) plasma ACTH concentrations were similar in the two groups. There were no significant differences in ACTH concentration between the two groups, although the mean values during and after surgery were somewhat greater in group $M_{0.1}$ than in group $M_{0.2}$ (fig. 6). In both groups, mean plasma concentrations of ACTH had increased significantly during and after surgery when compared with values during undisturbed anaesthesia ($P < 0.05$; $P < 0.01$) (fig. 6).

Plasma cortisol concentration (mean ± 1 SD) was similar in the two groups (fig. 7); in both, plasma cortisol concentration had increased during and 15 min after surgery when compared with the values obtained during undisturbed anaesthesia ($P < 0.05$; $P < 0.01$; $P < 0.001$).

DISCUSSION

Body weight and type of surgery performed were comparable in the two groups of children. Atropine was used as an anticholinergic since central sedative and amnesic effects are less with atropine than with hyoscine. The mean premedication time was about 15 min longer in group $M_{0.1}$ than in group $M_{0.2}$. This could mean that the peak effect of midazolam in group $M_{0.1}$ was over before the children arrived in the anaesthetic room and this could have had some influence on the sedative scoring. However, Vinik, Reves and Wright (1982) found that sedation was better at 60 min than at 45 min after the i.m. administration of midazolam. Fragen and colleagues (1983) also found that the decrease in anxiety was better at 90 min than at 60 min after the i.m. injection of midazolam. Thus the difference in the premedication times in the present study was not thought to affect significantly the evaluations of sedation and stress response.

In the group of children receiving the higher dose of midazolam, sedative scores were better than in the children receiving the smaller dose. This showed, as has been demonstrated previously for diazepam (Brown and Dundee, 1968), that the sedative and anxiolytic effects of midazolam are dose dependent. Side effects of anxiolytic drugs also increase with greater dose and it is known that diazepam depresses the central regulation of respiration—decreasing the carbon dioxide response (Catchlove and Kafer, 1971; Jordan, Lehane and Jones, 1980) and inspiratory drive (Clerque et al., 1981). Although studies similar to those cited for diazepam have not yet been undertaken with midazolam, the close chemical relationship between the various benzodiazepines and, in particular, between diazepam and midazolam (Reves, Corssen and Holcomb, 1978) suggests that the same neuropharmacological mechanisms would be involved in their actions. That is, one would expect midazolam to depress respiration in a dose-dependent manner.

However, end-tidal carbon dioxide concentrations measured in the anaesthetic room immediately after induction of sleep were similar in the two groups. This did not suggest a more profound respiratory depressant effect of midazolam 0.2 mg kg^{-1}, although sedative scores were higher and plasma catecholamine concentrations lower during undisturbed anaesthesia when the higher doses were used. Furthermore, the respiratory pattern before and during surgery was characterized by a somewhat lower minute ventilation and respiratory rate in group $M_{0.2}$, while E'_{CO_2} was unchanged between the two groups (fig. 2). This indicated a more favourable respiratory pattern with the higher dose, since lower respiratory rates are known to reduce wasted ventilation under similar conditions (Rose and Froese, 1980; Lindahl, Hulse and Hatch, 1984). Moreover, both groups in this study responded adequately to the inhalation of carbon dioxide just before the recovery period (2 h after administration of midazolam). Minute ventilation and tidal volume increased equally and respiratory rates were virtually unchanged—demonstrating a similar responsiveness to carbon dioxide in both groups.

The relationship between changes in $\dot{V}_E$ and E'_{CO_2} (fig. 4) revealed, in some of the children receiving the higher dose of midazolam, a slightly reduced ventilatory response to carbon dioxide. Thus, theoretically, a dose-dependent depression of the response to carbon dioxide similar to that found previously for diazepam (Catchlove and Kafer, 1971; Jordan, Lehane and Jones, 1980; Clerque et al., 1981), might exist. However, the number of patients in this study (which was designed primarily to evaluate the effects of the premedication) was too small to demonstrate conclusively the dose-dependent effect of midazolam on the regulation of breathing. This needs to be elucidated in further studies designed to examine this particular point.

The differences in respiration found between the two doses was small and, since no sign of serious respiratory depression was found before, during or after surgery when the dose of midazolam was increased from 0.1 to 0.2 mg kg^{-1}, the latter dose seems to be safe in such children. Therefore, use of the larger dose for premedication in normal children seems to be justified when one considers the beneficial effects on sedation and plasma catecholamine concentrations during undisturbed anaesthesia. However, plasma concentration of all hormones increased in the postoperative period—an effect resulting, most probably, from a lack of analgesia, which emphasizes the need for the early management of postoperative pain if anxiolytic drugs are used alone for premedication.

The increase in the dose of midazolam from 0.1 to 0.2 mg kg^{-1} i.m. resulted in a better preoperative sedation, in a lower plasma catecholamine concentration immediately after induction, and improved preoperative respiratory pattern. A dose-dependent respiratory depression of the response to carbon dioxide was evident for up to 2 h after the administration of the premedicant. Clinically, however, the ventilatory response to carbon dioxide after surgery was considered to be adequate in both groups. For premedication in children similar to those in this study, an i.m. dose of midazolam 0.2 mg kg^{-1} seems to be justified. However, the dose should be reduced in those patients with muscle weakness or at risk from neurologically depressed respiratory reflexes.

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We thank the anaesthetists and surgeons at the Hospital for Sick Children, Great Ormond Street, London, for their co-operation. We are also grateful to Roche Products Ltd for financial support of the study and in particular for the help of Dr D. Looi, Clinical Research Physician.

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DOUBLE-BLIND EVALUATION OF A LIGNOCAINE–PRILOCAINE CREAM (EMLA) IN CHILDREN

Effect on the Pain Associated with Venous Cannulation

E.-L. MAUNUKSELA AND R. KORPELA

SUMMARY

The effect of the topical application of a lignocaine–prilocaine cream (EMLA) on the pain of venous cannulation was tested in a double-blind manner. Sixty boys and girls between the ages of 4 and 10 yr who were to undergo surgery participated in the study. No analgesic premedication was given and the venous cannulation was performed during the preparation for general anaesthesia. Pain was assessed by the anaesthetist and the patient using a verbal rating scale and two different pictorial scales. The effect of EMLA in the alleviation of the pain of venous cannulation was considered significantly better than placebo by both anaesthetist ($P < 0.001$) and patient ($P < 0.05$) (verbal scales). One conventional pictorial scale showed a statistically significant difference ($P < 0.05$), but the other, based on facial expressions, did not. Local reactions to the cream were minor and transient in both groups.

Fear and pain can make i.v. cannulation a traumatic experience for a child, and time consuming for the clinician or nurse. It is a special problem in children with chronic diseases such as leukaemia, who undergo repeated blood sampling or i.v. injection. A topical preparation applied to the skin without discomfort which alleviated the pain of the needle puncture would be helpful to both patients and staff.

The solid, pure bases of lignocaine and prilocaine, if mixed in equal amounts, form an oil at temperatures greater than 16 °C; that is, they constitute a eutectic mixture. An oil-in-water emulsion cream of that mixture, EMLA (Eutectic Mixture of Local Anaesthetics), has been tested previously in adults (Ehrenström Reiz, Reiz and Stockman, 1983; Wahlstedt et al., 1984; Hallén, Carlsson and Uppfeldt, 1985) and in older children (Hallén and Uppfeldt, 1982; Ehrenström Reiz and Reiz, 1982). Although our clinical experience with the preparation in the paediatric haematology/oncology ward has been promising, these children tend to be prejudiced against all kinds of procedure. Therefore, we decided to study the tolerance and efficacy of the local anaesthetic cream on young children scheduled for elective surgery under general anaesthesia.

PATIENTS AND METHODS

Sixty boys and girls (aged 4–10 yr; ASA groups I or II) participated in the study (table I). No child had to be excluded because of suspected allergy to local anaesthetics.

The study was performed in accordance with the principles of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital, University of Helsinki. All

TABLE I. *Distribution of sex, age, body weight and premedication in the study groups*

	EMLA ($n = 30$)	Placebo ($n = 30$)	*P*
Boys/girls	15/15	22/8	ns
Age (yr) (mean ± SD)	6.4 ± 1.92	7.1 ± 1.86	ns
Weight (kg) (mean ± SD)	24.1 ± 9.42	22.8 ± 6.06	ns
Premedication			ns
None	6	2	
Flunitrazepam	13	19	
Diazepam	11	8	

E.-L. MAUNUKSELA, M.D.; R. KORPELA, M.D.; The Children's Hospital, University of Helsinki, Helsinki 29, Finland.

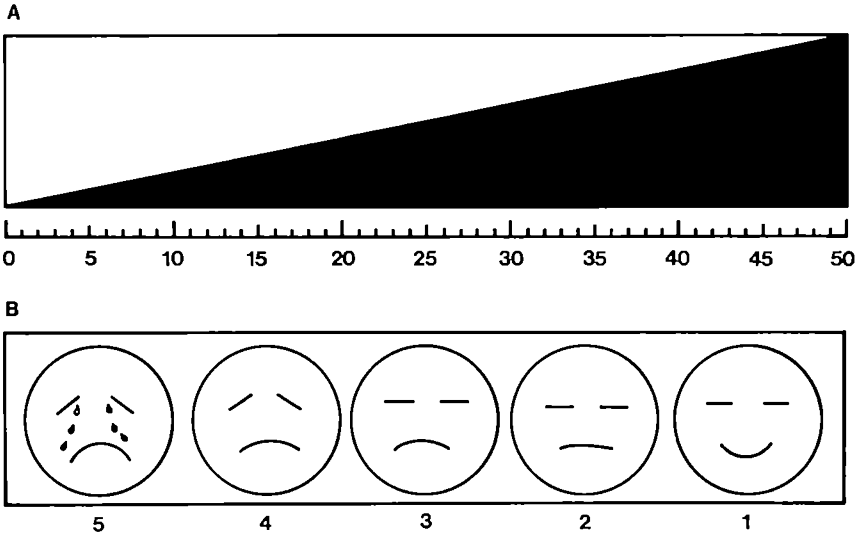

FIG. 1. Visual scales used for subjective evaluation of pain in The Children's Hospital, University of Helsinki. Scale A is 50 × 10 cm, and coloured bright red and white (Tammisto, Tigerstedt and Wirtavuori, 1983). Scale B has been designed in our hospital for use in young children. The left extreme of scale A and face 1 in scale B are defined as "no pain", the opposite ends of each scale as "pain as bad as it could possibly be".

the patients or their parents, or both, gave informed consent to the study.

The children were allocated randomly to treatment with either EMLA or placebo, with 30 in each group. Each millilitre of the EMLA cream contained lignocaine 25 mg and prilocaine 25 mg and in the placebo cream the eutectic mixture of local anaesthetics was substituted by Miglyol R 812 oil. The formulations were visually and cosmetically identical and they were packed in identical, numbered 5-ml aluminium tubes.

The design of the study and the rating scales (see below) were explained during the pre-operative visit and examples were given to verify that the child could use the scales. Premedication, diazepam 0.5 mg kg^{-1} by month or flunitrazepam 0.5–1.0 mg kg^{-1} up to 2.0 mg (by mouth) was given to 24 children in the EMLA group and to 27 in the placebo group (table I).

At least 60 min before the anticipated time of cannulation, a thick layer (2 g) of cream from a numbered tube was applied over the selected vein. The cream was covered with a thin plastic sheet (Glad R, Union Carbide) to form an occlusive dressing. Immediately before the insertion of the cannula the bandage was removed, and the skin was wiped dry and inspected for any local reaction. The skin was then disinfected with 0.5 % chlorhexidine in 70 % alcohol and the vein was cannulated with a Venflon 0.8- or 1.0-mm cannula.

Pain on cannulation was assessed, first, by the anaesthetist and then by the patient using a verbal rating scale of none, slight, moderate or severe. The patient was then asked to assess the pain using two different pictorial scales (fig. 1).

Differences between EMLA and placebo groups were tested by the Mann–Whitney test with rank sums and variances corrected for ties when appropriate.

RESULTS

One child was withdrawn from the placebo group; venous cannulation was not performed because the child was very anxious and unco-operative. There were no differences between the groups in size of cannula used, site of cannulation and the time for which the cream was applied. Local reactions after EMLA and placebo comprised slight redness in two and no children, and slight blanching of the skin in 11 and nine children, respectively. One patient receiving EMLA developed moderate blanching. All reactions disappeared within 1 h, except slight blanching in one patient receiving EMLA, in whom it lasted for 2 h.

Verbal assessments of pain are shown in figures

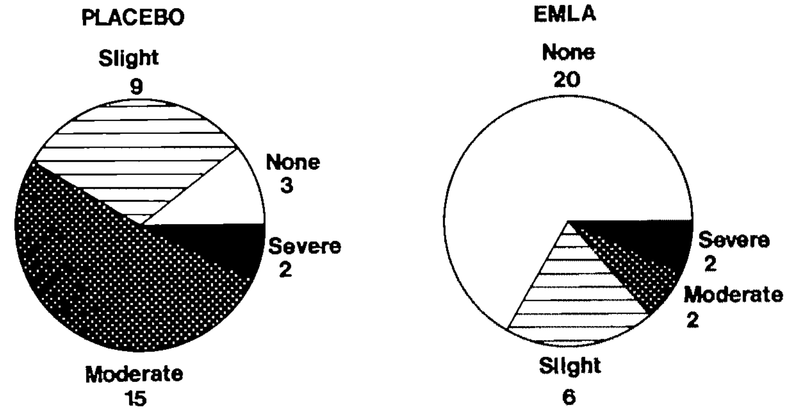

FIG. 2. Verbal rating of pain associated with cannulation as determined by the anaesthetist ($P < 0.001$).

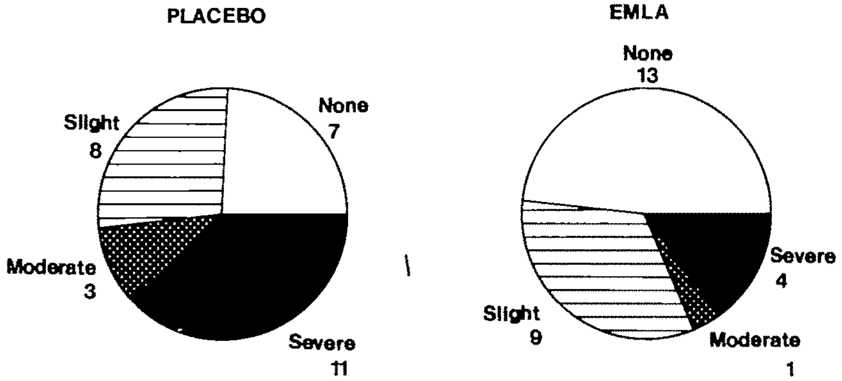

FIG. 3. Verbal rating of pain on cannulation as indicated by the patient ($P < 0.05$).

2 and 3. Three patients in the EMLA group were unable to co-operate with the verbal rating of pain. The differences in pain on cannulation between the EMLA and the placebo groups, as evaluated by the anaesthetist and the patient, were significant ($P < 0.001$ and $P < 0.05$, respectively).

Assessments using the pictorial scales 1 and 2 (fig. 1) were carried out in 21 and 22 children in the EMLA group and 25 and 27 in the placebo group, respectively. The remaining children were unable or unwilling to co-operate. On the red and white, linear scale the mean (median) figures in the EMLA and placebo groups were 12.4 (4) and 23.5 (22.5), respectively. The differences were significant ($P < 0.05$). There was no difference between the two groups when the degree of pain was assessed using the facial expressions.

DISCUSSION

Children learn to be afraid of all kinds of injections at a very early age (Mather and Mackie, 1983). For children with chronic diseases this becomes a major problem. Extreme fear can make minor procedures very traumatic for the child and time consuming for the personnel involved (Jay, Ozolins and Eliot, 1983). It would be preferable to avoid this, but until recently there has been no effective remedy.

In the earlier studies of EMLA in paediatric patients (Ehrenström Reiz and Reiz, 1982; Hallén and Uppfeldt, 1982) the mean age of the children was between 10 and 11 yr. However, in our opinion children who are too young to accept reasoned explanations would benefit most from an effective topical preparation of local anaesthetic.

Additionally, we wished to have the child's subjective evaluation of the degree of pain. Children between 4 and 10 years of age can localize and indicate the severity of pain (Eland, 1974) and, usually, understand the visual scales (own unpublished observations).

In the present series the efficacy of EMLA cream in alleviating the pain of venous cannulation was significantly better than placebo. The anaesthetist's evaluation was slightly more in favour of EMLA than the patient's (figs 2 and 3). From the technical point of view, a moderate or severe reaction to pain interferes with cannulation.

There were more young children in the EMLA group than in the placebo group; however, the difference in age was not significant (table I). Three of the four children in the EMLA group who considered the pain on cannulation severe were 4 yr and one 5 yr. When the patients' verbal assessments of pain were analysed according to age, there was no difference between EMLA and placebo in children aged 4–6 yr ($n = 28$). On the other hand, all the 7–10 yr old children ($n = 28$) in the EMLA group, and 43 % in the placebo group, reported no or slight pain ($P < 0.001$, Mann–Whitney *U* test). This result correlates well with the findings of Katz, Kellerman and Siegel (1980) and Jay, Ozolins and Eliot (1983). Children older than 7 yr can understand the meaning of medical procedures and display dramatically less overt distress than younger children, who have a strongly emotional attitude.

Although most of the children were premedicated, an analgesic was not used. While it might have been ideal to study the efficacy of the local anaesthetic without any premedication whatsoever, we felt that the preoperative situation was potentially distressing for young children and thought that a calm, premedicated child would concentrate more on the study than an anxious one. In some cases, premedication was too heavy and the child was unable to co-operate. However, there was no difference in the verbal rating of pain between the premedicated and un-premedicated children in the EMLA group.

Local reactions were insignificant and disappeared rapidly: one lasted for less than 2 h and all others disappeared within 1 h. The slight blanching seen with both EMLA and placebo creams was perhaps partially caused by the moisture under the occlusive bandage. The reactions did not correlate with the duration of application, which was at least 60 min, as recommended by Hallén, Olsson and Uppfeldt (1984). A shorter time would be advantageous in acute situations, but the 60-min application time was easy to arrange in conjunction with premedication. Our current clinical experience is that the local anaesthetic effect lasts several hours after the removal of the occlusive dressing and the cream.

The present study confirmed the local anaesthetic effect of EMLA cream in alleviating the pain of venous cannulation in young children. Local adverse effects were minimal.

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CHANGES IN DIAPHRAGMATIC POSITION IN ASSOCIATION WITH THE INDUCTION OF ANAESTHESIA

G. B. DRUMMOND, P. L. ALLAN AND M. R. LOGAN

SUMMARY

Images of a saggital section of the right hemidiaphragm were obtained using an ultrasound sector scanner in 20 patients in the supine position immediately before, and after, the induction of anaesthesia (with thiopentone). In the awake patient, the mean excursion of the part of the diaphragm that showed the greatest tidal movement was 1.56 ± 0.52 (SD) cm. The end-expiratory position of this part of the diaphragm was noted before and after induction. Craniad movement of this position was seen in 10 patients. In a further eight, the end-expiratory position did not change, and in two patients it moved caudally. The mean movement was 0.36 ± 0.52 cm in a cranial direction, which was statistically significant ($P < 0.01$) but was only 23% of the movement associated with quiet breathing. The extent or direction of movement was not related to the weight of the patient (expressed as a proportion of the expected weight). The findings do not support the hypothesis that the reduction of lung volume on induction of anaesthesia is caused solely by movement of the diaphragm.

When anaesthesia is induced in subjects who are supine, functional residual capacity (FRC) decreases by about 20% on average (Marsh, Southorn and Rehder, 1984). This decrease is probably an important factor in the impairment of gas exchange during anaesthesia—although this matter remains controversial (Dueck, 1984). Froese and Bryan (1974) reported evidence of the craniad movement of the diaphragm when anaesthesia was induced in two volunteers, and suggested that this movement was responsible for the decrease in FRC. In six volunteers, Hedenstierna and colleagues (1985) found that the dome of the diaphragm was more cranial during anaesthesia with artificial ventilation of the lungs than before anaesthesia. Furthermore, Bryan and his colleagues demonstrated, with cutaneous electrodes, that the induction of anaesthesia was associated with a loss of tonic activity in the diaphragm (Muller et al., 1979). The decrease in FRC caused by the induction of anaesthesia occurs rapidly (Bergman, 1982)—a finding which is consistent with a loss of muscle tone associated with the loss of consciousness. Relaxation and craniad movement of the diaphragm should cause a decrease in intra-abdominal pressure. During the induction of anaesthesia, measurements of gastric pressure as an index of intra-abdominal pressure showed decreases in most patients, but in five out of seven patients who were overweight, gastric pressure increased (Drummond and Park, 1984). This suggested that the major change in tonic activity in patients was in the ribcage muscles such as the intercostals.

The present study was undertaken to measure diaphragmatic movement on induction of anaesthesia using techniques other than radiography as estimation of the shape of the diaphragm by radiography can be difficult because of the overlapping of images (Marsh, Southorn and Rehder, 1984). We wished to confirm the previous findings of Froese and Bryan (1974) in a larger number of patients, and to assess the relationship of the measured movement to body weight.

PATIENTS AND METHODS

The study was approved by the local ethical advisory committee. Twenty patients (ASA

G. B. DRUMMOND, M.D.; P. L. ALLAN, M.D.; M. R. LOGAN, M.D.; Departments of Anaesthesia and Medical Radiology, Royal Infirmary, Edinburgh EH3 9YW.
Correspondence to G.B.D.

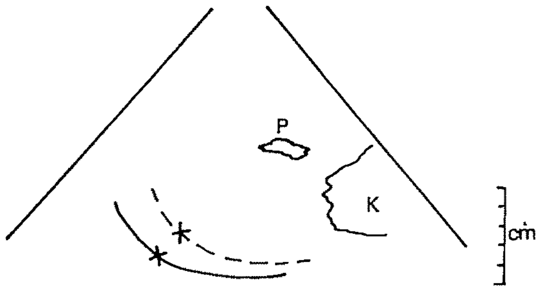

FIG. 1. Tracing of a representative ultrasound image. This shows a sagittal section of the right hemidiaphragm in a supine subject. It is seen as if from the right side of the subject, with the cranial direction on the left side of the image. P = porta hepatitis; K = perirenal fat. The extent of movement of the diaphragm during quiet breathing is shown: —— = end-expiration; —— = end-inspiration.

physical status I or II) about to undergo routine general anaesthesia and surgery gave their informed consent. They received temazepam 20 mg orally 1 h before the induction of anaesthesia. After measurements of heart rate and arterial pressure, an i.v.infusion was established and each patient was allowed to relax in the supine position, with the head slightly raised on a pillow. They were asked to breathe normally and allowed at least 5 min to become stable.

A 3.5-MHz realtime ultrasound sector scanner was used to provide an image of the right hemidiaphragm in the saggital plane. Whenever possible, an anterior subcostal approach was used, but in subjects in whom bowel gas obscured the diaphragm, an intercostal probe position was chosen. A section of diaphragm showing the most movement during quiet respiration was identified. This was always near the most dependent part of the dome. A cursor was placed at this point when the diaphragm was in the end-expiratory position. During inspiration, the curvature tended to become less, and this part of the diaphragm moved not only caudally, but also anteriorly (fig. 1). A second cursor was then placed on the diaphragm at the end-inspiratory position, so that the two points were placed on a common radius of diaphragmatic curvature. The second point was always caudal and anterior to the first. The diaphragmatic movement associated with tidal breathing (DM_{V_T}) was taken as the difference between these points, and was measured by the scanner to the nearest mm. Displacement in a caudal direction was expressed as a positive value.

Anaesthesia was induced with thiopentone 2–5 mg kg^{-1} i.v., given slowly via the infusion in an attempt to prevent apnoea. When the patient lost consciousness, the jaw was supported gently and oxygen given via a face mask, so that the breathing pattern could be seen and airway obstruction detected and corrected. When breathing became regular, the new end-expiratory position was noted with another cursor and the difference between the awake and anaesthetized positions measured (DM_{an}).

To relate these measurements to the degree of obesity of the patient, body weight was expressed as a percentage of the expected weight for a subject of the same age, sex and height (Geigy, 1956). This percentage is called %EW. Statistical presentation was by calculation of arithmetic means and standard deviation. However, parametric tests of statistical significance were not applied because the measurements of movement did not appear normally distributed. The Wilcoxon rank sum and Fisher's exact test were used to assess statistical significance (Campbell, 1974).

To assess the reproducibility of measurements of the position of the diaphragm, three male volunteer subjects were studied. Each subject lay in the supine position, wearing circumferential induction coil bands (similar in principle to that manufactured by Respitrace, but constructed locally). These coils give a signal proportional to the cross sectional area encompassed. One coil was placed at the nipple level and the other just below the level of the umbilicus. The signal from these coils was displayed to the subject on an oscilloscope and the subject was trained to breathe so that minimal changes in ribcage circumference occurred. Consequently, almost all the volume displacement during this pattern of breathing was associated with diaphragmatic descent. The subject breathed from a spirometer (Wedge, Med Sci) and the volume and inductance signals were recorded on a u.v. oscillograph (Bell and Howell Unigraph). An ultrasound image of the right hemidiaphragm was obtained and the cursor point placed on the diaphragm when it was approaching, but not at, the end-inspiratory position, so that the diaphragm moved through this position towards the end of inspiration. Each subject then breathed, with minimal ribcage excursion, with deliberate slight variations in tidal volume. The ultrasound operator was unable to observe the recording of the spirometer signal, but was able to impose marker signals on the recording at the time when he judged the diaphragm to be at the position

TABLE I. *Details of patients and movement of the diaphragm during tidal breathing and on induction of anaesthesia. — = Craniad*

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	%EW	Diaphragm movement (cm) Tidal	Diaphragm movement (cm) Induction
1	F	53	156	65	107	1.2	−1.0
2	F	35	157	65	114	0.9	−0.4
3	F	57	170	80	113	1.4	0
4	M	41	188	62	71	1.7	−0.8
5	M	67	180	79	97	2.5	−0.5
6	M	28	178	92	124	1.5	−1.0
7	F	43	160	52	88	1.0	0
8	F	66	159	75	130	0.8	−0.5
9	F	18	163	53	95	1.8	+0.5
10	F	40	168	55	85	1.4	0
11	F	51	152	78	139	2.2	0
12	M	24	185	78	99	1.0	0
13	M	20	170	60	95	2.7	0
14	M	28	182	76	98	1.5	−0.7
15	F	56	155	64	116	1.0	−0.8
16	M	33	168	69	106	1.3	0
17	F	46	156	54	96	1.8	−1.0
18	F	45	173	62	107	1.8	−1.4
19	M	48	188	80	96	1.8	0
20	M	70	171	72	107	2.0	+0.4
Mean		43.4	169	68.6	104	1.56	−0.36
SD		15.4	12	11.1	16	0.52	0.52

indicated by the cursor on the ultrasound display. This procedure differed from that used in the measurements made in the patients, so that consistent results could not be ensured by the presence of a constant breathing pattern. The variability in the measurements of spirometer volume obtained at the time the diaphragm was in the position indicated by the cursor was taken as a measure of the reproducibility of the measurements of diaphragmatic position.

RESULTS

In the three volunteers studied, the standard deviations of the volume that was judged by the ultrasound operator to be associated with a predetermined diaphragmatic position were 15, 39 and 56 ml.

The characteristics of the patients and the movements of the diaphragm are given in table I. Ages ranged from 18 to 70 yr and height from 152 to 188 cm. Weight varied considerably, from 53 to 92 kg, and %EW showed a similar range, from 71 to 139.

The movements of the diaphragm in patients during tidal breathing are shown in figure 2. The

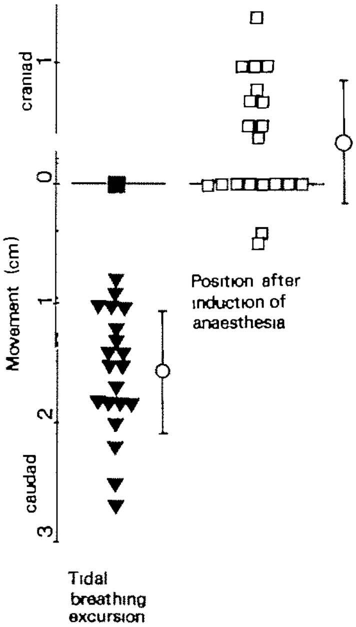

FIG. 2. Comparison of movements of diaphragm during tidal breathing ▼, from the end-expiratory position ■ before anaesthesia, and the change in end-expiratory position □ on induction of anaesthesia for the individual patients, with mean and SD of these movements.

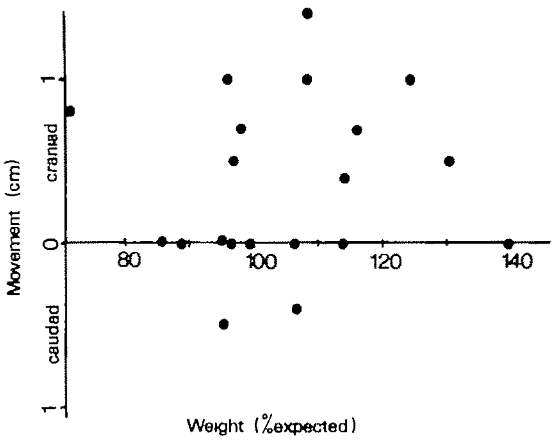

FIG. 3. Relationship between movement of end-expiratory position of the diaphragm on induction of anaesthesia, and patient weight (% expected).

range of movement varied from patient to patient, with a slight skew of the distribution towards greater values. The mean ($\pm$SD) movement was 1.56 ± 0.52 cm. There was no relationship between DM_{V_T} and age, height, and %EW, but a trend toward smaller movements was apparent in short and overweight patients. If these factors were considered together, a significant association was present. Patients whose height was less than the median (170 cm) and whose weight was also greater than expected, were significantly more likely to have tidal diaphragmatic movement less than the median value of 1.5 cm ($P < 0.05$).

The end-expiratory position of the diaphragm changed significantly after the induction of anaesthesia (mean DM_{an} -0.36 ± 0.52 cm, $P < 0.01$). However, no change was seen in eight of the 20 patients, and in two patients the actual movement was in a caudal direction. The movement was not linearly related to age or height and, in particular, there was no obvious relationship with %EW (fig. 3).

DISCUSSION

Cineradiography was used in a previous study of this phenomenon, but it involved exposure to radiation which can only be reduced by using modern image intensifiers. Radiographic apparatus can be cumbersome in clinical circumstances and a proposed study, in which we intended to use radiographic image intensification to investigate anaesthesia in volunteers, met with ethical objection.

Because of these considerations, ultrasound was used. The image obtained had the advantage of being unequivocally a unique segment of the diaphragm, but had the theoretical disadvantage that the segment chosen might not have been representative. However, in practice, the operator had ample opportunity to search for a representative segment and adjust the probe position to ensure satisfactory measurement. In all the subjects studied, the tidal movements measured were representative of movements seen in the remainder of the hemidiaphragm. The apparatus was easily used in the clinical setting before routine anaesthesia, involved minimal risk, and was tolerated well by the patients.

Since complete relaxation and quiet breathing were desirable, no attempt was made to instruct the patients about their breathing pattern, or to measure their tidal volume, as an awareness of breathing or the presence of measuring apparatus such as a mask or mouthpiece are known to alter the breathing pattern. However, measurements undertaken in similar patients in the same circumstances with a mask and spirometer have shown tidal volumes of the order of 600–800 ml (Drummond, unpublished data). The patients in the present study had respiratory frequencies between 15 and 20 b.p.m., which are consistent with tidal volumes of this size.

The position of the diaphragm is best related to an immobile landmark such as vertebral body. No such landmark was used in this study. However, observations in similar patients (Logan et al., 1985) have shown that the movements of the body frame that occur on induction of anaesthesia are usually small. In addition, in the present study, the ultrasound probe was held still deliberately during the induction of anaesthesia. In volunteers, the variability in the measurements was small. In the patients, it is likely that the variability of estimation of the position, at the end of the respiratory phases, would have been less, since the "target" was temporarily stationary. In addition, in the volunteers some variation in volume could have been the result of the small and inconsistent changes in ribcage circumference that could not be eliminated by training.

As in other studies of the phenomenon of FRG change, an unobstructed airway had to be maintained to avoid possible artefact. This was easily done with the use of gentle jaw support and head tilt, while observing the reservoir bag of the Magill breathing system to judge ventilation.

Temporary airway obstruction occurred in some patients, but no measurement was made until unobstructed respiration was obtained.

Tidal breathing

The excursions of the diaphragm found in this study were similar to those reported in a study that used anteroposterior fluoroscopy in supine conscious subjects. Wade (1954) reported a mean movement of the dome of the right diaphragm of 1.7 ± 0.2 cm during quiet respiration with a mean tidal volume of 758 ± 161 ml. This corresponds with our own measurements of tidal volume in similar patients. As might be expected, the tidal movements were less in short and overweight subjects. Sampson and Grassino (1983), in a study of normal subjects and overweight patients, found that tidal volume was inversely related to %EW.

In the present study, despite some variation between patients, in the depth of breathing, it seems likely that the mean DM_{V_T} of 1.56 cm would be associated with a mean tidal volume of the order of 700 ml. This is a little greater than, but of the same order as, the mean decrease of FRC that would be expected (about 500 ml).

Induction of anaesthesia

Although no exact measurements were made, the time course of the changes in the position of the diaphragm that were observed corresponded to the time course of other presumably related factors such as the end-expiratory position (Bergman, 1982) and gastric pressure (Drummond and Park, 1984).

Can the observed change in diaphragmatic position explain the change in FRC that usually occurs? Assuming, over the small range of movements studied, that a linear relationship exists between movement of the dome of the diaphragm and volume displacement, the mean reduction of lung volume would be about 23% of tidal volume. Even if the tidal volume had been unnaturally large, say 1 litre, this would still only account for about half the expected decrease. In addition, craniad movement occurred in only 10 of the patients studied, so in the other subjects a different mechanism has to be sought to explain the possible decrease in FRC.

Evidence for persistent end-expiratory activity in the diaphragm has been presented by Bryan and his colleagues (Muller et al., 1979), but has not been observed by others (Agostoni, Sant' Ambrogio and Carrasco, 1960; Druz and Sharp, 1981). Simpson and Grassino (1983) found that diaphragmatic activity could persist for up to 50% of the duration of expiration in massively obese subjects (300 %EW), but they did not report activity persisting to end-expiration.

Shifts in blood volume have been suggested as another possible cause of the changes in FRC (Jones et al., 1979; de Troyer and Martin, 1983), but direct measurements have not been able to confirm this as a single explanation (Hedenstierna, Johansson and Linde, 1982).

It is possible that the premedication (temazepam), although insufficient to cause any somnolence, might have already resulted in some reduction in FRC in the patients in the present study. However, the observations made by Bergman (1982) were made in premedicated patients.

The interactions between the length of the diaphragm, the position of its dome, lung volume and the dimensions of the abdomen and ribcage are complex (Mead and Loring, 1982). In a theoretical analysis, these workers suggested that the length of the diaphragm is not as closely related to the motion of the abdominal wall as was previously assumed, as the ribcage acts in part as a container for the abdominal contents so that ribcage expansion can "take up" abdominal contents. According to their analysis, if lung volume were to decrease, but there were no change in the length of the diaphragm, the ribcage would get smaller. This could occur if the ribcage muscles were to relax: the abdomen would get slightly larger, and the dome of the diaphragm would move slightly craniad. These predictions are supported by some of the observations of Jones and his colleagues (1979) and by our own studies (Logan et al., 1985). Hedenstierna and colleagues (1985) obtained CT scans in volunteers before and during anaesthesia. They found that the cross-sectional area of the thorax was reduced and that the dome of the diaphragm moved craniad by 1.9 cm ± 0.5 cm (mean and SEM). These findings are similarly consistent with the predictions of Mead and Loring (1982).

However, in their calculation of the volume of the abdomen, Hedenstierna and colleagues (1985) did not fully take into account the volume of the abdominal cavity that is enclosed by the lower part of the rib cage. They found that the lower rib cage was reduced in cross-sectional area after the induction of anaesthesia. Clearly, this represents a decrease in the volume of the abdominal container at this point. This change in volume provides an equally valid alternative explanation for some of the changes in volume that they calculated and chose to attribute to changes in blood volume. However, exact comparison of that study, in which the subjects were paralysed and ventilated, with the present study in which patients were studied during spontaneous ventilation, is unlikely to be fruitful. It would seem, on the basis of the analysis of Mead and Loring (1982), that the movements of the diaphragm seen in the present study can be explained by a loss of intercostal muscle tone alone. Further observations are being undertaken to substantiate this possibility, for which data are presently scarce (Marsh, Southorn and Rehder, 1984).

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CONTINUOUS INFUSION OF FENTANYL OR ALFENTANIL FOR CORONARY ARTERY SURGERY

Plasma Opiate Concentrations, Haemodynamics and Postoperative Course

M. HYNYNEN, O. TAKKUNEN, M. SALMENPERÄ, H. HAATAJA AND J. HEINONEN

SUMMARY

Nine patients received a mean total dose of 110 $\mu g\ kg^{-1}$ of fentanyl and 10 patients received alfentanil 1379 $\mu g\ kg^{-1}$ as a continuous infusion during coronary artery bypass grafting (CABG). Circulatory stability was well maintained through the induction of anaesthesia and a similar cardiovascular course was achieved with both agents, with the exception of small differences in heart rate and cardiac index immediately before tracheal intubation. Similar haemodynamic responses to sternotomy, cardiopulmonary bypass and awakening from anaesthesia were found with both analgesics. Although the times to awakening and extubation were somewhat shorter in patients receiving alfentanil, the differences between the groups were not significant. With the continuous infusion techniques, plasma opiate concentrations could be maintained well above the awakening values during cardiopulmonary bypass. In a total dose ratio of 1:13, fentanyl and alfentanil produced similar haemodynamic profiles and clinical courses in patients undergoing CABG.

High-dose fentanyl anaesthesia was introduced by Stanley and Webster (1978), who used an average total dose of 74 $\mu g\ kg^{-1}$ during cardiac surgery. Since then the method has been used widely, mean doses of up to 162 $\mu g\ kg^{-1}$ being administered (Wynands, Townsend et al., 1983), to patients undergoing coronary artery bypass grafting (CABG). However, when the dose of fentanyl is given principally during the induction of anaesthesia, the blood and brain concentrations of the drug may decrease below the anaesthetic concentration later in the operation—especially after the period of cardiopulmonary bypass (CPB) (Moldenhauer and Hug, 1982). The use of continuous infusion has been shown to provide more stable plasma fentanyl concentrations during all stages of cardiac surgery (Moldenhauer and Hug, 1982; Wynands, Townsend et al., 1983) and to prevent intraoperative hypertensive responses, especially those which occur during CPB, more effectively than the bolus technique (Wynands, Townsend et al., 1983).

Prolonged postoperative respiratory depression may be considered as a disadvantage of high-dose fentanyl anaesthesia (Lunn et al., 1979; Wynands, Townsend et al., 1983). Alfentanil, having a shorter duration of action than fentanyl (Brown, Pleuvry and Kay, 1980; Niemegeers and Janssen, 1981; Hynynen et al., 1985), might be devoid of this side-effect. Thus it might be suitable as an anaesthetic for patients undergoing cardiac surgery when given as a continuous infusion (de Lange, Stanley and Boscoe, 1981). To our knowledge, a parallel comparison of high-dose fentanyl and alfentanil infusion techniques within the framework of one study has not been performed. Therefore, we compared the haemodynamics and postoperative course in patients subjected to CABG, and receiving a continuous infusion of fentanyl or alfentanil.

PATIENTS AND METHODS

Patients

Nineteen patients scheduled for elective CABG were randomly anaesthetized with either fentanyl

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MARKKU HYNYNEN, M.D.; OLLI TAKKUNEN, M.D.; MARKKU SALMENPERÄ, M.D.; JUSSI HEINONEN, M.D.; Department of Anaesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki, Finland. HELENA HAATAJA, M.SC., Research Laboratories, Orion Pharmaceuticals Co., Espoo, Finland.

Correspondence to M.H.

or alfentanil. The patients had given their consent to the study, which had been approved by the institutional ethics committee. Patients with significant valvular disease or critical narrowing of the left main coronary artery, and those having an ejection fraction of less than 0.40 were excluded. Calcium channel blocking and beta-adrenergic blocking drugs were continued until the morning of the operation.

Anaesthesia

Lorazepam 0.06 mg kg^{-1} was given i.m. 2 h before the induction of anaesthesia. On arrival in the operating theatre, an i.v. infusion of Ringer's acetate–gluconate solution was commenced. A radial artery cannula and a flow-directed pulmonary arterial thermodilution catheter (Edwards Laboratories) were inserted under local anaesthesia (1% lignocaine). During cannulation the patients received 7.5 ml kg^{-1} of the Ringer's solution and during the induction of anaesthesia this solution was given at a rate of 3 ml kg^{-1} h^{-1}. Later i.v. fluids were administered as required to maintain cardiac filling pressures at their normal values.

Anaesthesia was induced with either fentanyl (Orion Pharmaceuticals, Finland) or alfentanil (Orion Pharmaceuticals, Finland) 48 μg kg^{-1}, the former being injected over 10 and the latter over 2 min. Simultaneously with this loading dose, a continuous infusion of the analgesic was started. Fentanyl was given at a rate of 0.3 μg kg^{-1} min^{-1} until rewarming was instituted (via the extracorporeal circulation), whereafter the infusion rate was 0.15 μg kg^{-1} min^{-1} until the end of operation. Alfentanil was infused at respective rates of 6 and 3 μg kg^{-1} min^{-1}. After consciousness was lost, pancuronium 0.1 mg kg^{-1} was administered. Ten minutes after starting the induction of anaesthesia, the trachea was intubated. Before intubation, ventilation was assisted or controlled manually when necessary by giving 100% oxygen via an anaesthetic face mask and a non-rebreathing valve. After intubation, ventilation was controlled with a mixture of oxygen and air ($F_{I_{O_2}}$ 0.5) using the non-rebreathing circuit of a Servo 900 B ventilator. The respiratory rate was 12 b.p.m. and the minute volume was adjusted to maintain Pa_{CO_2} between 4.8 and 5.9 kPa. The degree of neuromuscular blockade was estimated visually according to the train-of-four principle, using 2 Hz supramaximal stimulation of the ulnar nerve. Incremental doses of neuromuscular blocker were given to maintain blockade within 90–95%.

Cardiopulmonary bypass (CPB)

CPB was conducted with a roller pump (Gambro HL 10) and a bubble oxygenator (Shiley 100 A). The oxygenator was primed with 2000 ml of Ringer's acetate–gluconate solution. Non-pulsatile pump flow was maintained at 2.4 litre min^{-1} m^{-2} and Pa_{CO_2} within normal range. Mild systemic hypothermia (30–32 °C) was used and the haematocrit was maintained around 20–25%. The perfusion pressure was maintained between 50 and 90 mm Hg by giving small increments of phenylephrine or phentolamine, as required. Myocardial protection was achieved with cold St Thomas' type cardioplegic solution and topical cooling. At the termination of CPB the patients were rewarmed to a nasopharyngeal temperature of 37 °C. After bypass, the effect of heparin was reversed with protamine sulphate.

After surgery the patients were ventilated (IMV Bird-ventilator) using a positive end-expiratory pressure of 5 cm H_2O. Pa_{CO_2} was maintained between 4.8 and 5.9 kPa.

Plan of investigation

V_5-Lead of the ECG was monitored continuously and various limb leads intermittently. Haemodynamic measurements were performed before the induction of anaesthesia (control values), after induction but before intubation, after intubation, before the surgical incision, and at maximal sternal spread. After the operation, haemodynamic variables were recorded during the steady state before awakening and immediately after awakening. The measurements included heart rate (HR), systolic and mean arterial pressures (SAP, MAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO). If SAP exceeded 160 mm Hg, nitrous oxide in oxygen ($F_{I_{O_2}}$ 0.5) and nitroglycerin (by infusion) were administered, in that order, to decrease the pressure to less than 160 mm Hg. Phenylephrine, ephedrine or dopamine were used to increase SAP to greater than 90 mm Hg. Increments of propranolol 0.5 mg or glycopyrrolate 0.2 mg were administered if HR was greater than 100 or less than 40 beat min^{-1}, respectively.

The patients were considered to be awake when they could give correct responses to two consecutive questions by moving their head or limbs. Extubation was performed when all of the following criteria were fulfilled: good co-operation, stable cardiovascular dynamics, IMV rate 2 b.p.m. or less, spontaneous respiratory rate 10 b.p.m. or more, arterial pH within normal range and Pa_{CO_2} less than 6.0 kPa.

Measurements

Intravascular pressures were measured with AE 840 (AME) transducers which were calibrated against a water column. The midthoracic level served as the zero reference point. The pressures were recorded on an ink-jet recorder (Mingograf 804, Siemens-Elema) and the pressures were read at end-expiration.

Cardiac output was measured using the thermodilution method (Finnomedical cardiac output computer Model 804). Ten millilitre of normal saline at room temperature was injected at end-expiration. The mean of values derived from three well-formed thermodilution curves was included in the results. The reproducibility of the method was examined by calculating differences about the mean of repeat awake determinations and was 1.5 ± 0.2 (SEM)%. Cardiac index (CI), stroke index (SI), systemic (SVR) and pulmonary (PVR) vascular resistances, and rate–pressure product (RPP) were calculated using standard formulae.

Blood samples for the measurement of the concentrations of fentanyl and alfentanil were drawn from the radial artery at predetermined intervals. Plasma concentrations of fentanyl and alfentanil were analysed by capillary gas chromatography developed to allow the rapid determination of their plasma concentrations. Alfentanil and fentanyl were added as internal standards for each other, because they were not administered simultaneously. Extraction was performed from 1.0 ml of plasma at pH 12.0 with hexane–ethanol (19:1) 3.0 ml. The organic layer was evaporated to dryness and the residue was dissolved into 100 µl of a mixture of pentadecane (purity > 99%) (Fluka AG, Switzerland) and ethyl acetate (19:1). An aliquot of 0.5 µl was injected to the gas chromatograph. Analyses were performed with a Hewlett–Packard 5730A gas chromatograph equipped with an HP 1874 B capillary column control unit (Avondale, U.S.A.) and nitrogen sensitive detector. The temperature of the column (SE-30, 0.15 µm film, 12 m × 0.32 mm i.d.) (Orion Analytica, Espoo, Finland) was 245 °C. Injector and detector temperatures were held at 275 °C and 300 °C, respectively. With the helium flow rate of 3 ml min^{-1}, retention times were 1.3 min for fentanyl and 2.1 min for alfentanil.

The lowest detectable amount of both fentanyl and alfentanil was about 5 pg with signal to noise ratio of 3 injected in spikeless mode. The limit of sensitivity was 1 ng ml^{-1}. Fentanyl and alfentanil were quantitated using linear regression calibration lines which were constructed daily and were linear over the studied ranges.

Precision was studied with spiked plasma samples at fentanyl concentrations of 2.5, 10 and 50 ng ml^{-1} and coefficients of variation ($n = 6$ at each level) were 8.3%, 5.4% and 2.7%, respectively. At alfentanil concentrations of 5, 400 and 1000 ng ml^{-1}, precision was 5.7%, 3.8% and 1.1%, respectively. Recovery was studied by analysing spiked plasma samples, to which internal standard was added after extraction and evaporation. Recovery of fentanyl at concentration of 25 ng ml^{-1} was 87 ± 6% (SD, $n = 6$) and that of alfentanil at concentration of 100 ng ml^{-1} was 72 ± 5% (SD, $n = 6$). The method is specific for fentanyl and alfentanil. In blank plasma or in patient samples there were no interfering peaks at the retention times of fentanyl or alfentanil.

Statistics

Analysis of variance with repeated measures design was used for statistical evaluation of intra-group haemodynamic changes. Dunnett's (1964) or Bonferroni's corrections were used for multiple comparisons, where appropriate. The *t* test for two independent samples was used to compare changes between the groups. Fisher's exact probability test was applied to non-parametric data. *P* values less than 0.05 were considered statistically significant. The results are expressed as mean ± SD.

RESULTS

The two groups were comparable (table I). The durations of infusion were 4.2 ± 0.7 h in the fentanyl group and 4.3 ± 0.9 h in the alfentanil group. The durations of surgery were 3.3 ± 0.7 h and 3.5 ± 0.9 h, and those of CPB 1.6 ± 0.5 h and 1.8 ± 0.6 h in the fentanyl and alfentanil groups, respectively. The total dose of fentanyl was 110 ± 10 µg kg^{-1} and that of alfentanil 1379 ± 274 µg kg^{-1}.

Plasma opiate concentrations

Plasma fentanyl and alfentanil concentrations are shown in figure 1. The commencement of CPB

TABLE I. *Characteristics of patients. Mean ± SD or number of patients*

	Alfentanil	Fentanyl
n	10	9
Sex (female/male)	2/8	1/8
Age (yr)	51 ± 6	49 ± 12
Weight (kg)	78 ± 11	86 ± 10
Body surface area (m^2)	1.9 ± 0.2	2.0 ± 0.2
Preoperative medication		
Beta-blocker	10	7
Calcium-channel blocker	3	3
Nitrates	6	8
Ejection fraction	0.60 ± 0.12	0.59 ± 0.15
Akinesia or dyskinesia of left ventricle	5	3
Number of occluded vessels	2.8 ± 0.4	2.7 ± 0.7

was associated with decreases in plasma opiate concentrations. At awakening from anaesthesia, mean plasma concentrations were: fentanyl 6.4 ± 2.1 (range 2.3–9.2) ng ml^{-1}; alfentanil 0.46 ± 0.19 (range 0.24–0.78) μg ml^{-1}.

Haemodynamics before CPB

There were no significant differences between the groups in the control haemodynamic values (table II).

After the induction of anaesthesia, MAP, MPAP and PCWP were significantly decreased in

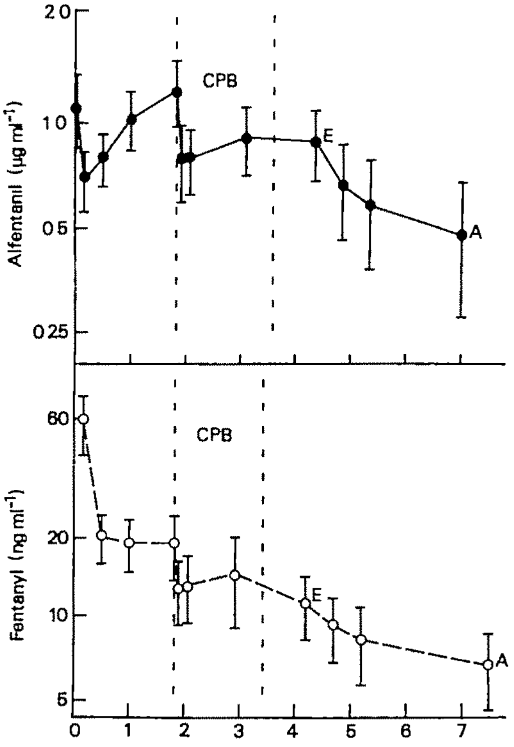

FIG. 1. Plasma opiate concentrations (mean ± SD) in patients anaesthetized for coronary artery bypass grafting surgery (continuous infusions of fentanyl or alfentanil). CPB = Cardiopulmonary bypass; E = end of opiate infusion; A = awakening from anaesthesia.

TABLE II. *Haemodynamic data before CPB (means and SD). Significant difference in the changes between the two groups*: †P < *0.05*; †††P < *0.001*. *Significant change from the control value within a group*: *P < *0.05*; **P < *0.01*; ***P < *0.001*. *AF = alfentanil; F = fentanyl*

	Control (awake)		After induction			After intubation		Before incision		Max sternal spread		
	AF	F	AF		F	AF	F	AF	F	AF		F
MAP	93.6	95.8	80.1**		84.6	87.5	84.3	72.4***	79.4*	87.9		98.6
(mm Hg)	6.3	8.7	11.2		14.2	16.4	14.1	11.9	12.0	13.9		10 1
MPAP	21.5	17.9	16.4**		19.4	20 6	20.1	15.5***	14.9	16.4**		17 6
(mm Hg)	4.6	6.2	3.4	†††	6.5	6 7	7.9	2.7	5.4	3.8	†††	6.1
PCWP	14.1	12.4	11 1*		12.7	11.6	13.3	7.9**	8.8	9.0*		8.7
(mm Hg)	3.7	5.2	4.3		6.1	4.1	5.8	2.9	3.8	4.2		3.0
CVP	6.2	5 2	6.0		5.9	6 1	6.0	4.3	4.9	5.5		5 6
(mm Hg)	1 5	2.2	2 6		1.7	2.2	2.6	1.8	2.5	2.4		2.3
CI	3.35	3 32	3.09		3.51	3.40	3 47	2.82*	3.08**	3.30		3.20
(litre min^{-1} m^{-2})	0.60	0.61	0.47	†	0.76	0.54	0.84	0.39	0 55	0.95		0.56
HR	65.3	66.6	64.1		72.3	70.4	72.8	65 1	69 2	69 1		71.6*
(beat min^{-1})	10.1	11.2	8 8	†	13.6	9.6	13.8	7.8	11 8	11 0		13.0
SI	52.1	50.4	49.2		49.0	48.8	48.1	43.9*	44.7*	47.5		45.7
(ml m^{-2})	10.7	8.3	10.4		9.0	7.6	10.8	7.0	6.1	9 3		9.8
SVR	1143	1152	1051		928**	1047	946**	1054	1005	1146		1209
(dyne s cm^{-5})	157	238	241		160	199	204	249	208	331		231
PVR	96.8	68.2	76 3		84.6	111.7	80.6	115.2	86.3	105.2		114 9*
(dyne s cm^{-5})	34.2	44.1	41.9		47.3	30.2	41.2	33.4	62.3	52.2		57.0
RPP	9042	9608	7635*		9103	9248	9126	7153**	7993	9028		10363
(mm Hg beat min^{-1})	1043	2070	1488		2052	2977	2064	1488	1488	2173		1915

the alfentanil group, but not in the fentanyl group, the changes in MPAP being significantly different between the groups (table II). CI decreased slightly in patients receiving alfentanil, whereas there was a small increase in this variable in the fentanyl group; as a result of these opposite changes, the difference between the groups was significant. This difference in CI seemed to be the result of a small decrease in SI in the alfentanil group and a significant intergroup difference in HR changes, there being a higher HR in the fentanyl group. The patients given fentanyl had a significant decrease in SVR, but this did not lead to a significant decrease in MAP, since CI was maintained.

After intubation, slight increases of MAP, MPAP, HR and CI were observed in the alfentanil group compared with values obtained after induction. Intubation produced no haemodynamic changes in patients receiving fentanyl and there were no intergroup differences between the changes from the control values at this stage of the study. However, when the changes from the postinduction values were compared, significant ($P < 0.05$) differences in MAP, HR and RPP were observed between the groups.

Immediately before the start of surgery, most of the haemodynamic indices (MAP, MPAP, PCWP, CVP, CI, SI and RPP) were at their lowest during the prebypass period. No intergroup differences were found.

At maximal sternal spread, MAP, CI, SVR and RPP increased moderately, reaching around the control value. The slight increase in HR compared with the control value was significant in the fentanyl group but not in the alfentanil group. CVP remained at its control value; PCWP was lower than at the control stage. The only significant difference between the two groups in the changes from control was that observed in MPAP, although the actual values were similar in the two groups at this stage of the study.

The number of patients who experienced significant changes in SAP and HR is presented in table III. The majority of the decreases occurred after the induction of anaesthesia and before the start of surgery, whereas the increases were observed after intubation and at maximal sternal spread. The total number of interventions caused by these haemodynamic changes was five in the alfentanil group (one patient was treated twice) and eight in the fentanyl group (ns). One patient in the alfentanil group had a significant depression of ST-segment (> 0.1 mV) in ECG before surgery.

Haemodynamics during CPB

Eight patients in both groups showed decreases in perfusion pressure which required treatment with phenylephrine. The total number of injections of phenylephrine was 25 in the alfentanil group and 23 in the fentanyl group. Increases in perfusion pressure requiring the administration of phentolamine were observed in one patient in the alfentanil group and three patients in the fentanyl group.

Haemodynamics at awakening

Haemodynamic measurements during the steady-state period before awakening were completed in eight patients from each group. The haemodynamic values obtained before and immediately after awakening in these 16 patients are presented in table IV. Before awakening, SI was significantly decreased from the awake control value in both groups, whereas HR was increased. The decreases in CI were not significant, but the decrease in MAP was significant in the fentanyl group. After awakening, MAP increased to the awake control value, HR remained increased and SI remained decreased in both groups. Awakening was associated with increases in MPAP and cardiac filling pressures, but only the CVP in the fentanyl group exceeded its awake control value significantly. The haemodynamic changes from the control values were not significantly different between the two groups.

Other postoperative data

The time required for the return of consciousness after the discontinuation of the infusion was 3.3 ± 1.2 (range 1.0–4.8) h in the fentanyl group and 2.6 ± 1.3 (range 0.8–4.1) h in the alfentanil group. Extubation was performed 14.4 ± 3.2 (range 10.0–18.3) h and 11.8 ± 3.5 (range 5.4–17.0) h after the end of opiate administration

TABLE III. *Number of patients requiring treatment for marked changes in systolic arterial pressure and heart rate during the various study periods before cardiopulmonary bypass*

	Alfentanil	Fentanyl
Increase in SAP	2	4
Decrease in SAP	2	2
Increase in HR	0	2
Decrease in HR	0	0

TABLE IV. *Control (awake) haemodynamic data (means and SD) compared with values obtained before and after awakening in eight patients receiving fentanyl and eight patients given alfentanil. Significant difference from the control value within a group:* *$P < 0.05$*;* **$P < 0.01$*;* ***$P < 0.001$*. Significant difference from the value obtained before awakening within a group:* §$P < 0.05$

	Control (awake)		Before awakening		After awakening	
	AF	F	AF	F	AF	F
MAP	93.3	97.4	77.9	75.5***	86.9	95.6
(mm Hg)	4.7	7.8	12.6	5.0	13.3	18.1
MPAP	22.6	17.0	18.5	16.0	23.3§	20.3§
(mm Hg)	4.4	4.5	3.0	3.9	3.8	2.4
PCWP	14.9	12.5	10.4	10.3	14.0§	16.0§
(mm Hg)	3.8	5.5	2.4	3.7	2.8	5.2
CVP	6.4	5.4	7.1	7.6	9.4	12.4*§
(mm Hg)	1.4	2.3	3.2	2.4	2.9	3.8
CI	3.30	3.41	2.46	2.49	2.78	2.91
(litre min^{-1} m^{-2})	0.66	0.42	0.54	0.77	0.62	1.01
HR	66.4	67.4	90.1**	91.1***	94.0**	100.6**
(beat min^{-1})	11.0	11.7	11.1	8.1	15.7	12.7
SI	50.5	53.0	25.3**	27.4***	30.4**	28.4**
(ml m^{-2})	11.6	6.6	9.0	7.4	9.5	8.9
SVR	1145	1153	1306	1230	1253	1324
(dyne s cm^{-5})	174	200	467	379	371	524
PVR	101.8	59.2	145.4	96.4	130.1	102.2
(dyne s cm^{-5})	33.7	24.0	53.2	66.8	58.5	95.7
RPP	9155	10283	9898	9451	11511	12976
(mm Hg beat min^{-1})	1065	1807	2219	1123	3382	3621

in the two groups, respectively. These differences were not significant.

DISCUSSION

The regimen by which fentanyl was administered in this study was modified from that described by Moldenhauer and Hug (1982). Alfentanil was administered as described by de Lange and colleagues (1981), de Lange, Stanley and Boscoe (1981) and Nauta and co-workers (1982). These regimens resulted in a total dose ratio of 13:1 between alfentanil and fentanyl. Fragen and colleagues (1984) suggested that alfentanil and fentanyl are equipotent when administered in a 10:1 total dose ratio by combining a priming bolus dose and a continuous infusion. Scott, Ponganis and Stanski (1985) infused alfentanil or fentanyl until delta waves appeared in the EEG. In their study the total dose ratio was 10:1.

It has been suggested that plasma fentanyl concentrations between 15 and 20 ng ml^{-1} attenuate satisfactorily those haemodynamic responses which accompany CABG (Moldenhauer and Hug, 1982). Our results are in agreement with those of Sprigge and co-workers (1982). Fifty percent of their patients had a significant increase in HR or arterial pressure before CBP with plasma fentanyl concentrations between 15 and 20 ng ml^{-1}. Five of our nine patients receiving fentanyl showed significant increases in HR or SAP, or both, before CPB at a mean plasma fentanyl concentration of around 20 ng ml^{-1}. There were no significant differences in plasma fentanyl concentrations between the patients who did, or did not, demonstrate cardiovascular responses.

Although an increase in the dose of fentanyl will decrease the number of patients in whom there is a heart rate or arterial pressure response to noxious stimulation during CABG (Sprigge et al., 1982; Wynands, Townsend et al., 1983), even doses greater than 100 μg kg^{-1} administered before CPB do not totally block the haemodynamic response in all patients (Wynands, Townsend et al., 1983). Furthermore, even plasma fentanyl concentrations exceeding 30 ng ml^{-1} have not provided complete haemodynamic stability in all patients (Wynands et al., 1984). Thus, it might be reasonable to maintain a "baseline" anaesthetic state with a desired plasma fentanyl concentration (well above the concentration at awakening) which will assure an acceptable haemodynamic stability. The haemodynamic responses to noxious stimuli, if observed, may then be treated by means other than increasing the dose of analgesic (Wynands et al., 1984).

With bolus doses of fentanyl 60 μg kg^{-1} (Bovill and Sebel, 1980) or 75 μg kg^{-1} (Hug and Moldenhauer, 1982; Wynands, Townsend et al., 1983) administered before CPB, mean plasma drug concentrations less than 10 ng ml^{-1} have been measured during CPB. With continuous infusions, mean plasma fentanyl concentrations have ranged, depending on the dose, from around 10 to around 25 ng ml^{-1} during CPB (Hug and Moldenhauer, 1982; Sprigge et al., 1982; Wynands, Townsend et al., 1983). In our patients mean plasma fentanyl concentrations varied between 12.5 and 14.5 ng ml^{-1} during CPB—a value considerably greater than the awakening value (6.4 ng ml^{-1}).

The time course of the plasma alfentanil concentrations in our study resembles that in the study of de Lange and de Bruijn (1983), who also used an infusion of alfentanil. The optimum plasma alfentanil concentration for blocking the responses to various surgical stimuli has been suggested to be at least 1.0 μg ml^{-1} (de Lange and de Bruijn, 1983). In our patients, the mean plasma alfentanil concentration during sternotomy and surgery, before initiation of CPB, varied from 1.0 to 1.2 μg ml^{-1}. However, at the time of intubation the concentration was somewhat lower (0.7 μg ml^{-1}) and one of the 10 patients required intervention after intubation and one after sternotomy, because of an increase in SAP. In the study of de Lange and de Bruijn (1983), similar increase in SAP was observed in one of the 14 patients after intubation and in two patients after sternotomy.

The haemodynamic profiles before CPB were not greatly different in our fentanyl and alfentanil groups. Furthermore, they resembled those in several previous studies in which rather similar administration regimens for fentanyl or alfentanil were utilized (Sebel, Bovill and van der Haven, 1982; Sprigge et al., 1982; de Lange and de Bruijn, 1983; Wynands, Whalley et al., 1983). After induction, heart rate remained unchanged in our patients receiving alfentanil but increased slightly in the fentanyl group, this difference giving rise to a significant difference in cardiac index between the groups. We cannot present any explanation for this difference, but its clinical significance may be limited since, at later stages in our study, no such difference was observed.

Our findings concerning perfusion pressure during CPB are in accordance with previous studies. In these studies hypertensive episodes occurred less frequently when fentanyl was given as a continuous infusion instead of as a single bolus dose (Wynands, Townsend et al., 1983). Similarly, hypertension was infrequent when alfentanil was administered as a continuous infusion or when supplementary doses of alfentanil were given during CPB (de Lange, Stanley and Boscoe, 1981; de Lange and de Bruijn, 1983). Actually, a tendency to low perfusion pressure was observed in our patients. This finding was similar to that of de Lange and de Bruijn (1983), who had to discontinue the infusion of alfentanil periodically during CPB because of a decrease in arterial pressure.

In accordance with the EEG findings reported by Bovill and colleagues (1983), many of our patients awoke rapidly from anaesthesia. However, we found few significant haemodynamic changes on arousal.

Plasma fentanyl concentration at awakening (6.4 ng ml^{-1}) and the awakening time (3.3 h) in our fentanyl group were comparable to those reported by Moldenhauer and Hug (1982) and de Lange and co-workers (1982), respectively. Somewhat longer mean times of mechanical ventilation have been reported by Moldenhauer and Hug (1982) (19 h) and Wynands, Townsend and associates (1983) (19 h) than was necessary in our patients (14 h).

The mean duration of postoperative unconsciousness in our alfentanil patients (2.6 h) was in agreement with that reported by de Lange and de Bruijn (1983) (3.1 h), while de Lange, Stanley and Boscoe (1981) observed a somewhat shorter time (1.4 h). Our patients had a mean plasma alfentanil concentration of 0.46 μg ml^{-1} at awakening which was comparable to that reported by Bovill and colleagues (1983) (0.48 μg ml^{-1}), while de Lange and de Bruijn (1983) observed a concentration of 0.27 μg ml^{-1}.

In the study of de Lange, Stanley and Boscoe (1981) 14 of the 15 patients anaesthetized with alfentanil fulfilled the criteria for extubation within 5 h (4.1 ± 1.2 h) of the operation. Patients receiving alfentanil in this study did not meet our criteria for extubation until 11.8 ± 3.5 h after the end of the drug infusion. We are unable to explain this difference.

The precise equipotent doses of fentanyl and alfentanil, in man, are not clear (Cookson, Niemegeers and vanden Bussche, 1983). In addition, the different durations of action of fentanyl and alfentanil (Brown, Pleuvry and Kay, 1980; Niemegeers and Janssen, 1981; Hynynen et al., 1985) make it difficult to choose dose regimens for continuous infusions for comparison. Nevertheless, the dose schemes used in this study seemed to be about equally effective in suppressing the haemodynamic responses to noxious stimuli. Our results suggest that, when given in very large doses, alfentanil cannot be expected to have a short duration of action.

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CONTINUOUS INFUSION OF FENTANYL OR ALFENTANIL FOR CORONARY ARTERY SURGERY

Effects on Plasma Cortisol Concentration, β-Endorphin Immunoreactivity and Arginine Vasopressin

M. HYNYNEN, A-M. LEHTINEN, M. SALMENPERÄ, F. FYHRQUIST, O. TAKKUNEN AND J. HEINONEN

SUMMARY

Plasma cortisol, β-endorphin immunoreactivity (PBE_{ir}) and arginine vasopressin (AVP) responses during and after the continuous infusion of fentanyl or alfentanil were studied in 19 patients undergoing coronary artery bypass grafting (CABG). Plasma cortisol concentration decreased significantly in both groups during the anaesthesia and surgery before cardiopulmonary bypass (CPB); an increase was evident during CPB in both groups, but a statistically significant increase was not observed during the rest of the study, including the awakening from anaesthesia. PBE_{ir} increased with both opiates immediately after initiation of CPB and remained so during the rest of the study. There were no significant changes in plasma AVP concentrations during anaesthesia and surgery. After discontinuation of opiate infusions, an increase in AVP concentration commenced earlier in the alfentanil group than in the fentanyl group. At awakening from anaesthesia, a significant correlation was observed between log plasma AVP concentration and systemic vascular resistance. It is concluded that, with continuous fentanyl and alfentanil infusions in a total dose relationship of 1:13 in patients undergoing CABG, cortisol and AVP responses to surgery and CPB can be suppressed. However, during recovery from anaesthesia, the attenuating effect of alfentanil seems to wear off more rapidly than that of fentanyl. PBE_{ir} response to CPB and emergence from anaesthesia could not be prevented with either analgesic.

Plasma cortisol, β-endorphin immunoreactivity (PBE_{ir}) and arginine vasopressin (AVP) concentrations are increased as a result of the stress induced by surgical or anaesthetic procedures (Oyama and Kimura, 1970; Oyama and Takiguchi, 1970a; Lush et al., 1972; George et al., 1974; Philbin et al., 1977; Dubois et al., 1981; Traynor and Hall, 1981; Lehtinen et al., 1984). Such hormonal responses, especially the increases in catecholamine and AVP concentrations, could be harmful to patients with ischaemic heart disease (Kehlet, 1979; de Lange, 1982; Boyle et al., 1983). High-dose fentanyl anaesthesia has been shown to prevent the hormonal responses to stress in cardiac surgical patients up to the commencement of cardiopulmonary bypass (CPB) (Stanley et al., 1980; Kono et al., 1981; Sebel et al., 1981); only a partial effect was observed during CPB (Stanley et al., 1980; Sebel et al., 1981), while no suppression could be demonstrated by Walsh and colleagues (1981) in the postoperative period. It has been suggested that alfentanil might be more effective than fentanyl in suppressing such hormonal responses (de Lange et al., 1982).

In the fentanyl studies cited above, the total dose of the opiate was given either at the induction of anaesthesia or before the start of CPB. This

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Markku Hynynen, m.d., Markku Salmenpera, m.d., Olli Takkunen, m.d., Jussi Heinonen, m.d. (Department of Anaesthesia); Ann-Mari Lehtinen, m.d., m.sc. (Department of Anaesthesia at the Departments I and II of Obstetrics and Gynaecology); Frej Fyhrquist, m.d. (IV Department of Medicine); Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki, Finland.

Correspondence to M.H.

mode of administration may be associated with low plasma fentanyl concentrations during and after CPB resulting in responsiveness before the end of surgery (Hug and Moldenhauer, 1982; Moldenhauer and Hug, 1982). However, if fentanyl is infused continuously, a stable plasma drug concentration can be maintained for the duration of the operation, including the period of CPB (Moldenhauer and Hug, 1982; Sprigge et al., 1982; Wynands et al., 1983). Continuous infusion would be especially suitable for the administration of alfentanil because of its short duration of action (de Lange, Stanley and Boscoe, 1981). To our knowledge, hormonal stress responses to cardiac surgery have not been studied in association with a continuous opiate infusion technique. Therefore, we decided to compare infusions of fentanyl and alfentanil in regard to their ability to suppress cortisol, PBE_{ir} and AVP responses to the induction of anaesthesia, surgery, CPB and emergence from anaesthesia in such patients.

PATIENTS AND METHODS

Patients

Plasma cortisol, PBE_{ir} and AVP concentrations were studied in the same 19 patients presented in the first part of our study (Hynynen et al., 1986). Randomly allocated, 10 patients received alfentanil and nine were given fentanyl by continuous infusion.

Anaesthesia

Anaesthesia was started between 8.00 and 9.00 a.m. In the alfentanil group, anaesthesia was induced with alfentanil 48 $\mu g\ kg^{-1}$ given over 2 min. Simultaneously, a continuous infusion of alfentanil 6 $\mu g\ kg^{-1}\ min^{-1}$ was started and continued until the patient was being rewarmed when the infusion rate was decreased to 3 $\mu g\ kg^{-1}\ min^{-1}$ and continued at that rate until the end of the operation. Fentanyl was infused as follows: a loading dose of 48 $\mu g\ kg^{-1}$ was given over 10 min; the rate of the continuous infusion was 0.3 $\mu g\ kg^{-1}\ min^{-1}$ until rewarming and 0.15 $\mu g\ kg^{-1}\ min^{-1}$ thereafter until the end of the operation. (For further details of anaesthesia, CPB and postoperative treatment, see the previous paper (Hynynen et al., 1986).)

Blood sampling

Blood samples for cortisol, PBE_{ir} and AVP analyses were taken at the following stages of anaesthesia and surgery: after premedication and cannulation but before the induction of anaesthesia (C = control); 30 min after the start of induction (I-30); at maximal sternal spread (St); immediately before (P-0), and 15 min after (P-15), initiation of CPB; after rewarming to a nasopharyngeal temperature of 36 °C during CPB (P-W); 60 min after discontinuation of the opiate infusion (E-60); and at the time of awakening from anaesthesia (A).

Arterial blood for plasma cortisol and AVP analyses was collected into 10-ml EDTA tubes, whereas blood for PBE_{ir} determination was taken into polypropylene tubes containing heparin 2.5 µl and aprotinin 25 µl for each 1 ml of blood. The samples were centrifuged immediately and the plasma was stored at -20 °C (cortisol) or -70 °C (PBE_{ir} and AVP) until assayed.

Assay methods

Cortisol. Cortisol concentrations were measured by radioimmunoassay (Farmos Diagnostica ^{125}I-Cortisol Kit) as described earlier (Lehtinen, 1981). The normal range in adults is 200–800 nmol $litre^{-1}$ at 8.00–9.00 a.m. and 150–500 nmol $litre^{-1}$ at 3.00–4.00 p.m. The inter-assay coefficient of variation was 7.5 % and the intra-assay coefficient of variation as calculated on three pooled samples was 7.3–8.2 %.

β-Endorphin immunoreactivity. The total PBE_{ir} was measured using a radioimmunoassay technique described by Vuolteenaho and coworkers (1981). The characteristics of antiserum K2 have been described previously (Vuolteenaho et al., 1981). This antiserum detects the 1–21 portion of the β-endorphin molecule and crossreacts completely with β-lipotropin (β-LPH). The cross-reactivity of the antiserum is 15 % with γ-endorphin and less than 0.1 % with α-endophin, metor leu-enkephalin or ACTH. Thus, the PBE_{ir} comprises β-LPH, β-endorphin and its metabolites. The sensitivity of the assay was 4 pg/tube. The intra-assay and inter-assay coefficients of variation were less than 10 and 15 %, respectively.

Arginine vasopressin. Plasma AVP concentration was measured using a previously described radioimmunoassay method (Fyhrquist, Wallenius and Hollemans, 1976). Reference value by this method in healthy adults in the supine position is 2.0 ± 1.2 pg ml^{-1} (mean ± SD). Crossreactivity of AVP antiserum with oxytocin was less than 0.03 %, with pressionic acid less than 0.1 % and with the C-terminal tripeptide of AVP less than 0.2%. The detection limit was 0.2 pg. The intra-assay coefficient of variation was 8% and the inter-assay coefficient of variation was 14%.

Statistical analyses

Since the distributions of PBE_{ir} and AVP data were skewed, a logarithmic transformation was performed to achieve a normal distribution before analysing the data. Within the study groups, significant changes from the control values were identified using an analysis of variance with repeated measures design followed by the paired *t* test with Dunnett's correction for multiple comparisons with a control (Dunnett, 1964). The *t* test for two independent samples was used to compare changes between the groups. The linear regression analysis was used to assess the interrelationship between AVP concentration and some haemodynamic variables. *P* values less than 0.05 were considered statistically significant. The results are expressed as mean ±SEM.

RESULTS

The durations of opiate infusions were 4.2±0.2 and 4.3±0.3 h, of surgery 3.3±0.2 and 3.5±0.3 h and of CPB 1.6±0.2 and 1.8±0.2 h in the fentanyl and alfentanil groups, respectively. The haemodynamic profiles during the study were similar in the two groups (Hynynen et al., 1986).

The total doses of opiates infused were 110±3 $\mu g\ kg^{-1}$ for fentanyl and 1379±87 $\mu g\ kg^{-1}$ for alfentanil; the dose relationship was 1:13. The plasma fentanyl and alfentanil concentrations were presented in the first part of the study (Hynynen et al., 1986).

Cortisol concentration (fig. 1)

In the fentanyl group, the plasma cortisol concentration decreased significantly after induction of anaesthesia and remained decreased until the commencement of CPB. In the alfentanil group, the decrease in cortisol concentration reached statistical significance at the time of sternotomy. After the initiation of CPB, cortisol concentrations increased in both groups but, compared with control values, the increases were not significant. There were no statistically significant differences between the changes in the two groups, although after surgery the cortisol concentration tended to be higher in the alfentanil group.

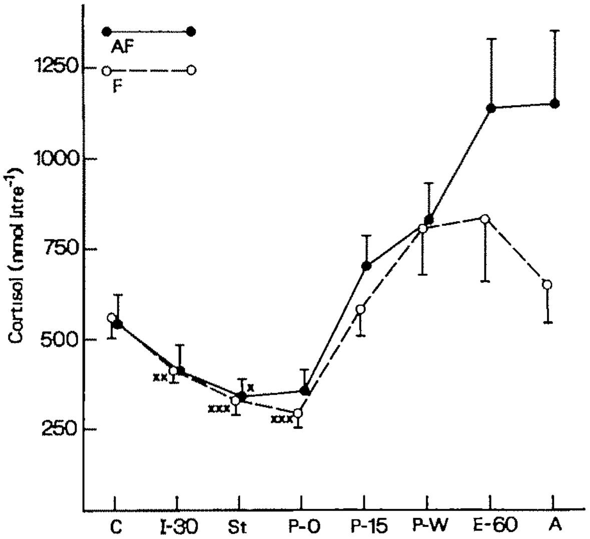

FIG. 1. Plasma cortisol concentrations in patients anaesthetized for coronary artery bypass grafting surgery with continuous infusion of fentanyl or alfentanil (mean and SEM). C = control value after premedication but before induction of anaesthesia; I-30 = 30 min after initiation of induction of anaesthesia; St = maximal sternal spread; P-0 = immediately before CPB; P-15 = 15 min after initiation of CPB; P-W = after rewarming at the end of CPB; E-60 = 60 min after discontinuation of opiate infusion; A = awakening from anaesthesia. In figures 1–3 the statistical significance is indicated as follows: ◇ = $P < 0.05$ between the groups; x = $P < 0.05$, xx = $P < 0.01$, xxx = $P < 0.001$ within the groups.

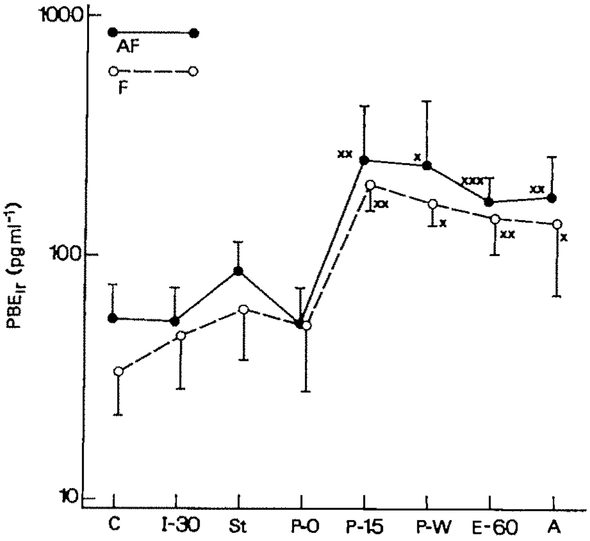

FIG. 2. Plasma β-endorphin immunoreactivity concentrations during high dose fentanyl or alfentanil anaesthesia (mean and SEM). (For explanations, see legend of figure 1.)

β-Endorphin immunoreactivity (fig. 2)

There were no statistically significant changes in PBE$_{ir}$ concentrations until the start of CPB. After the initiation of CPB, a significant increase in PBE$_{ir}$ occurred in both groups and increases in concentration were observed up to the end of the study. There were no significant differences between the two groups at any stage of the study.

Vasopressin concentration (fig. 3)

In the fentanyl group, AVP concentration remained unchanged throughout the study up to awakening, when an increase (not significant) was observed. The increase in AVP at awakening was statistically significant in patients given alfentanil. In addition, 60 min after discontinuation of the drug infusions, AVP concentration was significantly higher in the alfentanil group than in the fentanyl group.

Haemodynamic indices and vasopressin concentration (fig. 4)

A statistically significant relationship was found between log AVP and systemic vascular resistance (SVR) at awakening, but not at the control stage or during sternotomy. No significant correlation existed between AVP and mean arterial pressure or cardiac index at any of these stages of the study.

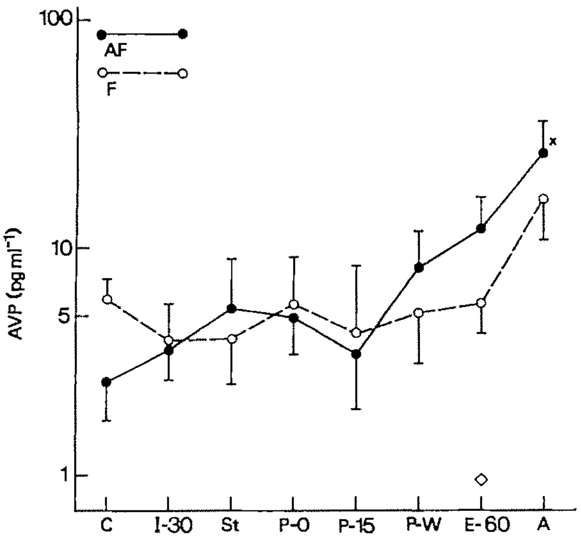

FIG. 3. Plasma arginine vasopressin concentrations during high dose fentanyl or alfentanil anaesthesia (mean and SEM). (For explanations, see legend of figure 1.)

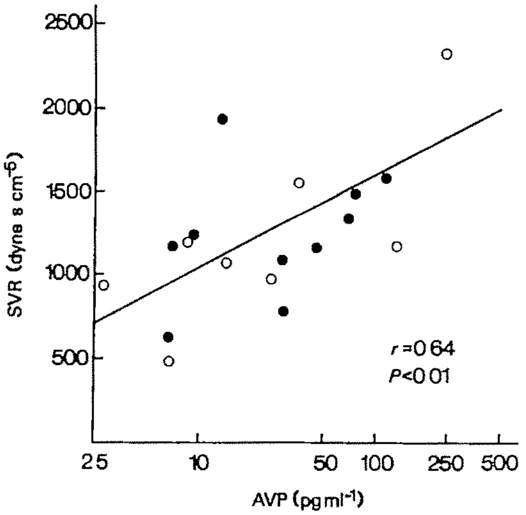

FIG. 4. Relationship between plasma arginine vasopressin concentration and systemic vascular resistance at awakening from high dose fentanyl (○) or alfentanil (●) anaesthesia.

DISCUSSION

The hormonal response to surgical stress is characterized by increases in the secretion of several hormones, such as cortisol (Lush et al., 1972), growth hormone (Oyama and Takiguchi, 1970b), antidiuretic hormone (Oyama and Kimura, 1970), catecholamines (Tammisto et al., 1973; Halter, Pflug and Porte, 1977) and aldosterone (Engquist et al., 1978). Recently, evidence has been accumulating that increases in PBE$_{ir}$ can also be regarded as an indicator of increased stress during various anaesthetic and surgical procedures (Dubois et al., 1981; Fukui, Hameroff and Gandolfi, 1984; Lehtinen et al., 1984).

Cortisol. During high dose fentanyl anaesthesia, our results concerning the plasma cortisol concentrations are consistent with those obtained previously (Stanley et al., 1980; Kono et al., 1981; Sebel et al., 1981; Walsh et al., 1981), when a conventional bolus technique was used. In our patients cortisol concentrations decreased before the start of CPB, but began to increase thereafter. This increase did not, however, reach significance during any of the study periods.

In the alfentanil group, too, cortisol concentrations decreased during the induction of anaesthesia and during the period of early surgery before

CPB. This finding agrees with the results of de Lange and colleagues (1983) who used a repeated bolus dose administration technique during CABG. In their study, however, cortisol concentration was significantly decreased also during CPB, while in our patients the cortisol concentrations were within control range in this period. This difference remains unexplained.

After the discontinuation of the narcotic infusions, plasma cortisol concentrations showed a further increase in the alfentanil group, but not in the fentanyl group. Although this increase did not reach statistical significance, it may suggest that alfentanil is shorter-acting than fentanyl in its suppressant effect on the cortisol response to surgical stress.

β-Endorphin immunoreactivity. $\mathrm{PBE_{ir}}$ responses to surgical stress have been suppressed by small doses of morphine (Dubois et al., 1981) and medium doses of fentanyl (10–20 μg kg^{-1}), but not with enflurane (Dubois et al., 1982). Lehtinen and coworkers (1984) could prevent the increase in $\mathrm{PBE_{ir}}$ in response to tracheal intubation by a deep level of anaesthesia or by topical analgesia. If $\mathrm{PBE_{ir}}$ is an indicator of hormonal stress response, CPB appeared to present an extreme degree of stress in our patients. However, our results agree with those of Yamashita and colleagues (1984), who demonstrated a significant increase in $\mathrm{PBE_{ir}}$ during CPB in paediatric patients undergoing open-heart surgery. Their patients were anaesthetized with droperidol, fentanylandnitrous oxide. On the other hand, in patients undergoing myocardial revascularization, Cork, Hameroff and Weiss (1985) could prevent the $\mathrm{PBE_{ir}}$ response to CPB with diazepam–fentanyl but not with diazepam–halothane anaesthesia. Whether the difference between their results and ours can be explained by the administration of diazepam before CPB, warrants further evaluation.

The activation of the endorphin system simultaneously with ACTH and cortisol (Guilleman et al., 1977; Dubois et al., 1981) seems to indicate its linkage to the hypothalamic–pituitary–adrenal axis. In our patients the concomitant release of cortisol and $\mathrm{PBE_{ir}}$ was not obvious. Therefore, it is possible that large doses of opiates have some direct depressant effect on the adrenal cortex. Unfortunately, we did not measure ACTH concentrations in our patients. On the other hand, the $\mathrm{PBE_{ir}}$ response to stress may be more difficult to block than the cortisol response.

Vasopressin. In the studies of the AVP response to CABG under high dose fentanyl anaesthesia, it has been possible to prevent the increase in AVP concentration during anaesthesia and surgery up to the commencement of CPB (Kono et al., 1981), but not during CPB (Stanley, Philbin and Coggins, 1979; Crone et al., 1982). The conventional intermittent administration model used in these previous studies could have led to low concentrations of fentanyl during CPB. Our results suggest that AVP responses can be attenuated when a continuous infusion of fentanyl with stable plasma fentanyl concentration is used during CPB.

The suppression of the AVP response during CPB in our alfentanil group is similar to the results of de Lange and colleagues (1982) who, by using a frequent alfentanil bolus technique, could prevent AVP responses to CPB in patients undergoing CABG. However, in our patients alfentanil could not prevent the increase in plasma AVP concentration at emergence from anaesthesia. This finding, together with the greater plasma AVP concentration in the alfentanil than in the fentanyl group 60 min after discontinuation of the infusions, seems to indicate that alfentanil is shorter-acting than fentanyl in its suppressant effect.

In the presence of increased plasma AVP concentrations at awakening of our patients there was a moderate correlation between AVP and SVR values. This finding agrees with the results of a previous study (Boyle et al., 1983). In addition, Pohjavuori and Fyhrquist (1980) observed a significant correlation between AVP concentration and systolic arterial pressure. High circulating plasma AVP concentrations may, therefore, increase the work load of the heart by increasing afterload. Furthermore, the potential capacity of high plasma AVP concentrations to cause coronary vasoconstriction should be considered. Although AVP is not the only factor determining left ventricular afterload, our results suggest that it would be advantageous if the attenuation of AVP response would extend into the postoperative phase.

In conclusion, when administered as a continuous infusion in a total dose relationship of 13:1, alfentanil and fentanyl were equally effective (during infusion) in attenuating the hormonal responses to the stresses associated with CABG. Our results suggest that AVP responses can be prevented also during CBP by using continuous infusion of opiates. After discontinuation of the infusions, the attenuating effect of alfentanil seemed to wear off faster than that of fentanyl. However, this difference did not seem to be associated with any notable difference in haemodynamic variables between the two patient groups.

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CHANGES IN PRESSOR HORMONE CONCENTRATIONS IN ASSOCIATION WITH CORONARY ARTERY SURGERY

Renin and Vasopressin Responses

S. HAWKINS, M. FORSLING, T. TREASURE AND W. AVELING

SUMMARY

In 10 patients undergoing routine coronary artery surgery, plasma renin activity and vasopressin concentration were measured at intervals before the induction of anaesthesia, and for 6 h after bypass. In three patients plasma renin activity was increased, but the increases followed no particular pattern. Vasopressin concentrations increased in all 10 patients, but the changes were not significantly correlated with the postoperative arterial hypertension that was seen in seven of the patients.

Systolic arterial pressures of greater than 140 mm Hg are a recognized sequel of coronary artery surgery and occur in 70% of patients (Cooper et al., 1985). If untreated, arterial pressures in excess of 200 mm Hg may be seen, sometimes with serious consequences—such as bleeding from the suture lines on the aorta or episodes of ventricular fibrillation. Such hypertension results from a progressive increase in systemic vascular resistance in the presence of a significant decrease in cardiac output (Estafanous et al., 1984), and is particularly undesirable after cardiac surgery because of the decrease in tissue perfusion and the increase in myocardial work which ensues.

Although the physiological mechanisms involved remain unclear, the stimulus to vasoconstriction seems evident. On starting cardiopulmonary bypass, the atria are rapidly emptied and arterial pressure decreases initially to 40–50 mm Hg, in spite of the maintenance of systemic flow. The resulting reflex vasoconstriction persists for some hours into the postoperative period, and is suggestive of a humoral cause.

Both arterial and atrial hypotension stimulate the release of vasopressin, the concentration of which has been shown to increase during cardiac surgery (Philbin et al., 1977; Simpson and Forsling, 1977; Wu, Zbuzeck and Bellevue, 1980). There has been interest in the effect of using a pulsatile form of arterial pump, with some authors claiming a significant decrease in the concentration of the hormone (Philbin et al., 1979; Levine et al., 1981), whereas others could find no difference (Frater et al., 1980). However, a review of the literature reveals a marked increase in vasopressin concentration in all the reports, with the similarities between the different studies being more impressive than the relatively small differences between the various groups (fig. 1). However, the vasopressin concentration has not been measured over a long period after the operation—when the problem of hypertension is most troublesome.

The juxtaglomerular apparatus is important in the control of arterial pressure, and the hypothesis that the increase in peripheral vascular resistance which persists after bypass is a result of stimulation of the renin–angiotensin system is attractive. Taylor and colleagues (1977) demonstrated increases in the concentration of angiotensin-II after bypass that were not evident after closed mitral valvotomy. However, other studies of the renin and angiotensin system and its relationship with cardiopulmonary bypass have been disappointingly inconsistent (Landymore et al., 1979; Watkins et al., 1979; Frater et al., 1980; Salerno et al., 1981).

In contrast, most workers who have studied

SIMON HAWKINS, M.B., B.S., F.F.A.R.C.S., W. AVELING, M.A., M.B., B.CHIR., F.F.A.R.C.S. (Department of Anaesthesia); MARY FORSLING, B.SC., PH.D. (Department of Physiology); TOM TREASURE, M.D., M.S., F.R.C.S. (Cardiac Surgical Unit); The Middlesex Hospital and Medical School, Mortimer Street, W1N 8AA.

Correspondence to T.T.

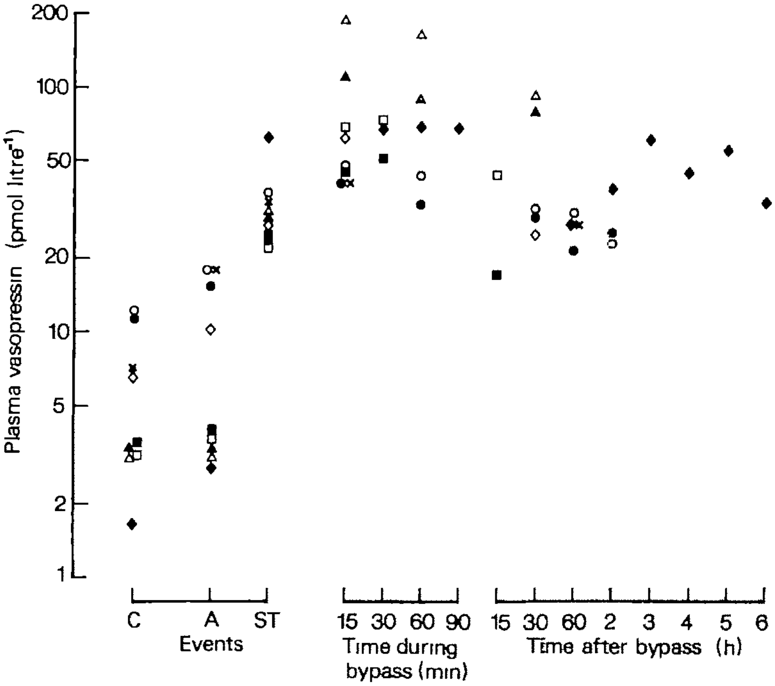

FIG. 1. A comparison of plasma vasopressin concentrations obtained by various groups of workers during cardiopulmonary bypass. C = control value; A = after anaesthesia; ST = after sternotomy. The values include results where the patients were on non-pulsatile bypass: □ = Philbin and colleagues (1977); △ = Levine and colleagues (1981); ○ = Frater and colleagues (1980); ◇ = Woods and colleagues (1983); and on pulsatile bypass: ■ = Philbin and colleagues (1977); ▲ = Levine and colleagues (1981); ● = Frater and colleagues (1980); and ◆ = present study.

catecholamines in this context, have found that they were increased in concentration during and after bypass. Landymore and co-workers (1979) found increases in catecholamine concentrations with no significant difference between pulsatile and non-pulsatile perfusion. Wallach and associates (1980), while finding that plasma renin activity did not correlate with arterial pressure, did show a positive correlation between the concentrations of adrenaline and noradrenaline and mean arterial pressure in the postoperative period. Roberts and colleagues (1977) in a series of 100 coronary artery by-pass operations demonstrated that perioperative hypertension caused by increases in systemic vascular resistance, was associated with increases in catecholamine concentrations and, furthermore, that these increases were greater in those patients who developed postoperative hypertension. Having also found increases in plasma renin activity, the same group (Niarchos et al., 1979) went on to study the effect of the angiotensin converting enzyme inhibitor (captopril) in 13 patients who were hypertensive after coronary artery surgery. It was effective in eight out of 13, the number of non-responders suggesting that postoperative hypertension must be multifactorial in origin.

Since it has been shown that relatively small increases in vasopressin in man produce changes in total peripheral resistance of 20–30% (Ebert et al., 1984) we chose to investigate changes in vasopressin concentration and plasma renin activity in an attempt to gain a better understanding of the aetiology of postoperative hypertension. Pulsatile bypass was used in all patients, since we believe this to simulate physiological perfusion most closely.

PATIENTS AND METHODS

Ten patients, aged 30–65 yr, undergoing elective coronary artery surgery were studied. Preoperative medication included beta-adrenoceptor blocking drugs, calcium channel blockers and nitrates. All patients had good left ventricular function as indicated by angiography, and had normal plasma urea and creatinine concentrations.

Premedication was with diazepam 10–20 mg by mouth 2 h before surgery and papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 1 h later. Anaesthesia was induced with thiopentone and papaveretum, and maintained using nitrous oxide in oxygen, lorazepam 4 mg immediately before bypass and incremental doses of papaveretum (0.5–1.5 mg kg^{-1} total dose). Halothane 0.5–1.0% was administered if the systolic arterial pressure was greater than 140 mm Hg while the patient was in the operating theatre. Pancuronium 0.2 mg kg^{-1} total dose was used to provide neuromuscular blockade.

Cardiopulmonary bypass (CPB) was between the right atrium and the ascending aorta, with a bubble oxygenator primed with Hartmann's solution 1.5 litre, a Stockert pump in the pulsatile mode and cooling to 28 °C. Cold potassium cardioplegia (St Thomas's Hospital) solution and topical cold saline were used to protect the myocardium during the period of aortic cross-clamping.

Mean perfusion pressure greater than 100 mm Hg was treated with phentolamine, and that less than 50 mm Hg with metaraminol. After bypass a systolic arterial pressure sustained at greater than 140 mm Hg, in spite of adequate sedation and correction of blood-gas tensions, was treated with sodium nitroprusside.

Samples were taken from an antecubital vein before the induction of anaesthesia and, subsequently, from a radial artery 15 min after induction; 15 min after sternotomy: at 30, 60 and 90 min during CPB; and 1, 2, 3, 4, 5 and 6 h after CPB. The samples were stored in crushed ice and cold spun, the plasma deep frozen and analysed within 14 days of sampling. Plasma renin activity was measured by radioimmunoassay by the generation of angiotensin-I at 37 °C at pH 5.5. Measurements of vasopressin concentration were undertaken on plasma extracted with bentonite using radioimmunoassay (Stromberg, Forsling and Akerlund, 1981). Vasopressin is not metabolized in the lungs (Lansome, 1974) and, therefore, venous and arterial samples are comparable.

Results were analysed using Wilcoxon's non-parametric tests and least squares linear regression.

RESULTS

The duration of aortic cross clamping ranged from 30 to 60 min (mean 47.8 min) and the total duration of bypass from 48 to 106 min (mean 83.7 min). Seven patients received an infusion of sodium nitroprusside in the postoperative period to control arterial hypertension.

In seven of the 10 patients the plasma renin activity changed little (fig. 2). In the remaining three, identified in the figure, increases were seen, but there was no clear pattern or correlation with mean arterial pressure. One had high control values—18 μmol litre^{-1} h^{-1}. This patient, although fitting the criteria for inclusion in the study on the basis of preoperative assessment, had features of poor cadiac output before the induction of anaesthesia and may not have been entirely comparable to the other patients.

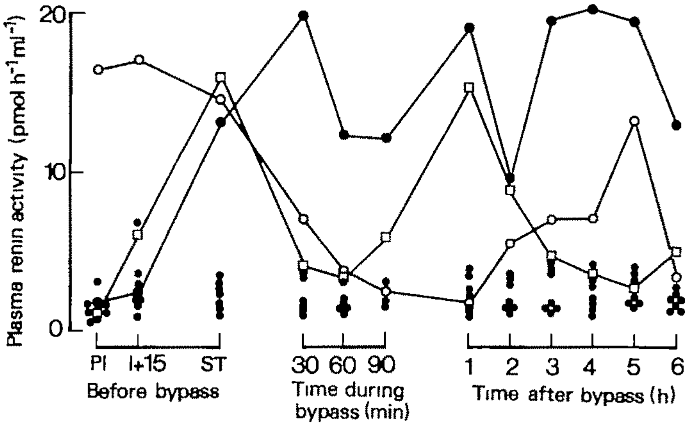

FIG. 2. Plasma renin activity in 10 patients undergoing coronary artery surgery. For the sake of clarity, the seven patients with little change in activity have not been identified individually. PI = Preinduction sample; I+15 = sample 15 min after induction of anaesthesia; ST = sample after sternotomy.

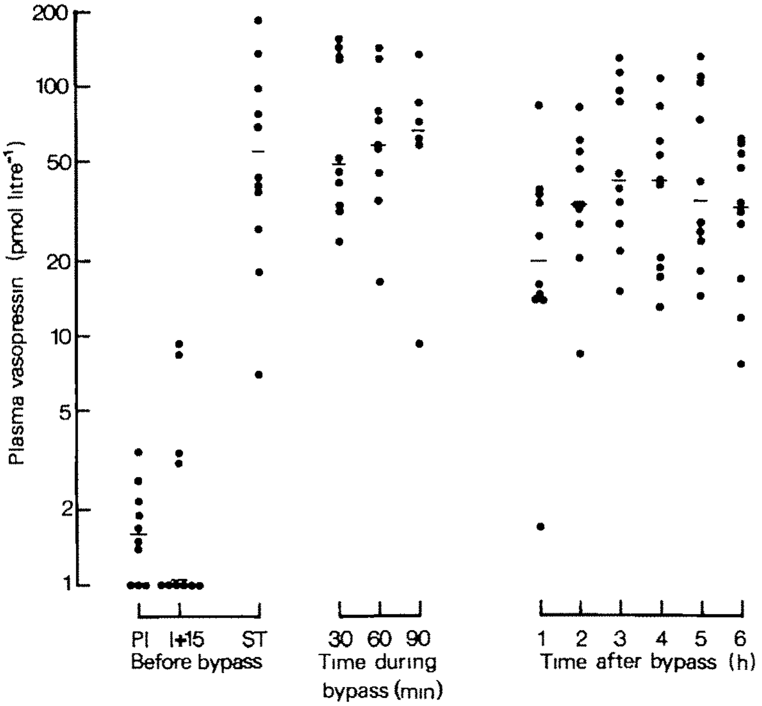

FIG. 3. Plasma vasopressin concentrations plotted logarithmically, with sample times as in figure 2, that is pre-induction (PI), 15 min after induction (I + 15), 15 min after sternotomy (ST), and during and after bypass.

Plasma vasopressin concentration (fig. 3) showed no significant change on induction of anaesthesia, but in all 10 patients increased from a median value of 1.0 pmol litre^{-1} to 56 pmol litre^{-1} (normal < 4 pmol litre^{-1}) 15 min after sternotomy ($P < 0.01$). Further samples 30, 60 and 90 min after initiating CPB showed no further change. One hour after CPB there was a significant decrease in plasma vasopressin concentration to a median value of 20.6 pmol litre^{-1} ($P < 0.01$). However, at 3 h after CPB the vasopressin concentration had increased significantly again, to 42.7 pmol litre^{-1} ($P < 0.01$). A significant correlation with arterial pressure was not demonstrated.

Urine output over the first 6 h after operation averaged 139 ml h^{-1} per patient (range for the 10 patients 115–291 ml h^{-1}). Specific gravity ranged from 1.010 to 1.016. No patient received diuretics, mannitol or inotropic support in the postoperative period.

DISCUSSION

The hypothesis that vasoconstriction and the resultant hypertension that occur so consistently after contemporary cardiopulmonary bypass are related to stimulation of the renin–angiotensin system has not been confirmed in our study. The work of Taylor and colleagues (1979), Watkins and co-workers (1979) and Landymore and associates (1979) described increases in angiotensin-II concentration or plasma renin activity, or both, which were attenuated to a significant extent by pulsatile bypass. Frater and colleagues (1980) also found increases in plasma renin activity, but the values reached a maximum before bypass, and the standard deviation of the samples taken during bypass was of a magnitude similar to the mean value for the 12 patients (229.1, SD 227.3), bringing the validity of the method of statistical analysis into question. Furthermore, in that series hypertension was not a feature, while Salerno and co-workers (1981) could find no increase in plasma renin activity with either type of bypass, but experienced a high incidence of hypertension. In our study, there were no changes in seven of 10 patients and the changes in the other three were so inconsistent that we have chosen to present the original data rather than to attempt an interpretation. It seems that any relationship between post-CPB hypertension and the renin–angiotensin system is tenuous and obscure.

In marked contrast, the concentration of vasopressin increased in every patient and the pattern was consistent. Furthermore, analysis of the data from other workers (fig. 1) shows a remarkable consistency; the similarities between the patients operated upon in New York (Frater et al., 1980), Boston (Philbin et al., 1977; Levine et al., 1981), Germany (Weidler et al., 1982) or London is more striking than any differences between groups of patients. Nevertheless, although the majority of our patients (7/10) developed hypertension, we were unable to demonstrate a correlation with the changes in vasopressin concentration.

The dilution of blood by the pump prime (1.5 litre) would affect the volume of distribution of vasopressin, which is about two-thirds of extracellular volume (Fabian et al., 1969). As fluid is continually being lost and replaced throughout the bypass, it was felt that an arithmetical correction would be meaningless. The vasopressin concentrations found in this study would be an underestimate of total hormone release, but not of concentration at the end organ.

Anaesthesia has been regarded as a stimulus to the release of vasopressin, but in spite of the use of opioids with premedication and induction we, like Philbin and co-workers (1976), did not observe this. The possibility that the renin–angiotensin system, through angiotensin-II, stimulates vasopressin has been reported (Padfield and Morton, 1977), but the fact that there was no increase in the concentration of renin in seven of our 10 patients would seem to preclude this as the mechanism of vasopressin release in this study. Previous writers have concentrated on the influence of bypass itself on the circulating concentrations of vasopressin. However, there are many intrathoracic receptors that could be implicated. The increase in vasopressin concentration noted in the present study occurred after sternotomy and no further significant increase was observed while on bypass. Although it was not remarked upon in their papers, we note that a similar increase had occurred, before bypass, in other studies (Philbin et al., 1977; Frater et al., 1980; Levine et al., 1981). Therefore, we have concentrated our attention on the timing of the increase in vasopressin concentration and in the accompanying paper (Knight et al., 1986) have sought to examine more precisely its relationship to other perioperative events.

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CHANGES IN PLASMA VASOPRESSIN CONCENTRATION IN ASSOCIATION WITH CORONARY ARTERY SURGERY OR THYMECTOMY

A. KNIGHT, M. FORSLING, T. TREASURE, W. AVELING, L. LOH AND M. F. STURRIDGE

SUMMARY

Plasma vasopressin concentrations in 14 patients undergoing coronary artery surgery were compared with those in eight patients undergoing thymectomy. Vasopressin concentrations increased similarly in both groups on sternotomy. A second, and more marked increase was noted in the patients requiring cardiopulmonary bypass. Haemodynamic stimuli could be responsible in both groups and might explain both the similarities and the differences between the groups.

The aetiology of postoperative hypertension following cardiopulmonary bypass (CPB), particularly when used during myocardial revascularization, remains obscure, although the renin–angiotensin system, and vasopressin, have been implicated. A previous investigation (Hawkins et al., 1986) failed to demonstrate any consistent pattern of change in plasma renin activity. However, in all patients plasma vasopressin concentration increased significantly after sternotomy and remained so for up to 6 h into the postoperative period. This release of vasopressin was stimulated not only by CPB but also by the events which preceded bypass.

Vasopressin is released rapidly after a trigger stimulus and has a circulating half-life of about 8 min (Fabian et al., 1969). As the purpose of this second study was to determine the stimuli to vasopressin release, the only non-cardiac operation routinely performed through a median sternotomy, thymectomy, was chosen for comparison. Sampling times were chosen to follow surgical events by 3 min. If the interval between samples was more than 15 min, a new baseline sample was taken.

PATIENTS AND METHODS

Two groups of patients were studied: 14 undergoing elective coronary artery surgery, and eight having a median sternotomy for thymectomy.

Coronary artery surgery

Twelve men and two women, aged between 40 and 73 yr (mean 54) were included in the study. All had normal renal and hepatic function; patients with poor left ventricular function (ejection fraction < 30%) were excluded. Preoperative medication included beta-adrenoceptor blockers ($n = 9$), diuretics ($n = 5$), isosorbide, persantin, nifedipine and nitrates. Premedication was with diazepam 10–20 mg by mouth, followed 1 h later by papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. A cannula was inserted to the radial artery under local anaesthesia and monitoring was instituted with a cardioscope and an automatic arterial pressure monitor (Dinamap). Anaesthesia was induced with papaveretum and thiopentone. The dose of opioid administered was standardized to total 1 mg kg^{-1} divided between the premedicant and the induction doses. After induction, the right internal jugular vein was cannulated and a catheter inserted to the bladder. The ECG, arterial pressure, central venous pressure and temperature were displayed throughout the procedure, and arterial blood-gas ten-

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Anne Knight, M.D., F.F.A.R.C.S., W. Aveling, M.A., M.B., B.CHIR., F.F.A.R.C.S. (Department of Anaesthesia); Mary Forsling, B.SC., PH.D. (Department of Physiology); Tom Treasure, M.D., M.S., F.R.C.S., M. F. Sturridge, M.S., F.R.C.S. (Cardiothoracic Unit); The Middlesex Hospital and Medical School, Mortimer Street, London W1N 8AA. L. Loh, F.F.A.R.C.S. (and M. F. S.), The National Hospitals for Nervous Diseases, Queen Square, WC1.

Correspondence to T.T.

sions, plasma concentrations of sodium and potassium, and urine volume, were measured regularly. Pancuronium was administered to provide neuromuscular blockade.

Anaesthesia was maintained with nitrous oxide in oxygen supplemented with halothane before bypass if the systolic arterial pressure increased above 150 mm Hg. The technique of bypass included a single right atrial cannula and arterial return to the ascending aorta; a bubble oygenator (Harvey or Bentley), primed with 1500 ml of lactated Ringer's solution; a roller pump (Stockert or Gambro) used in the pulsatile mode; arterial flow of 2.4 litre min^{-1} m^{-2}; and whole body cooling to 28 °C. During bypass the patient received lorazepam 4 mg and additional doses of pancuronium. Subsequent doses of opioid were withheld during bypass until all sampling was completed. Mean arterial pressure on bypass was kept between 90 and 50 mm Hg with phentolamine or metaraminol.

During aortic cross-clamping the myocardium was protected with St Thomas's Hospital cardioplegic solution and topical cooling with saline at 4 °C.

Twelve samples for the measurement of vasopressin concentration were taken from the arterial line, usually 3 min after each possible stimulus under investigation during the preparatory part of the operation and, then, before going onto bypass; after 3, 15 and 30 min of bypass; and, finally, 2 h after bypass (table I). Plasma and urine were collected for osmolality measurements after induction, during bypass and 2 h after bypass.

Thymectomy

Patients ($n = 8$) were all female, aged 18–52 yr (mean 32 yr), suffering from myasthenia gravis, and all were receiving treatment with anticholinesterases. They were premedicated with papaveretum and hyoscine. In the anaesthetic room 4% cocaine solution was applied to the nasal mucosa, anaesthesia was induced with thiopentone, suxamethonium was administered and the trachea intubated with a Portex nasal tube to permit long-term management. Anaesthesia was maintained with nitrous oxide, oxygen and halothane; spontaneous ventilation resumed at the end of the procedure.

The sternotomy incision was identical to that used for cardiac surgery, but the pericardium was not opened. The ECG and end-tidal $P\text{co}_2$ concentration were monitored throughout the procedure, and arterial pressure was measured

TABLE I. *Mean changes (SEM) in heart rate (HR), mean arterial pressure (AP) and central venous pressure (CVP) during coronary artery surgery and thymectomy*

	Coronary artery graft				Thymectomy		
Code	Event	HR (beat min^{-1})	AP (mm Hg)	CVP (mm Hg)	Event	HR (beat min^{-1})	AP (mm Hg)
1	Pre-induction	61 (3.7)	93 (4.2)	—	Pre-induction	79 (9.2)	88 (5.0)
2	Intubation +3 min	81 (5.1)	92 (7.8)	—	Intubation +3 min	96 (7.6)	98 (6.0)
3	Leg incis. +3 min	74 (3.9)	83 (4.3)	6 (1.1)			
4	Chest incis. +3 min	73 (4.8)	90 (4.3)	6 (1.3)	Chest incis. +3 min	65 (3.5)	77 (3.7)
5	Saw+3 min	74 (3.8)	100 (4.2)	4 (2.7)	Saw+3 min	72 (4.8)	86 (7.1)
6	Retraction +3 min	75 (3.7)	93 (6.4)	5 (1.3)	Retraction +3 min	66 (4.3)	77 (5.7)
7	Peric. tract+3 min	72 (3.4)	69 (6.2)	9 (1.8)			
8	Heparin (CPB-3)	83 (3.5)	87 (3.5)	5 (1.4)	Sternotomy +15 min	65 (3.1)	76 (6.8)
9	Bypass +3 min	—	49 (3.6)	3 (1.1)			
10	Bypass +15 min	—	50 (3.9)	1 (1.2)	Sternotomy +30 min	68 (4.0)	73 (4.3)
11	Bypass +30 min	—	62 (4.1)	3 (1.0)			
12	2 h post CPB	94 (4.3)	100 (3.1)	5 (0.8)	Postop.	68 (2.3)	89 (3.8)

automatically at 1-min intervals (Dinamap). Plasma osmolality was determined before and after surgery. Plasma vasopressin concentration was assayed in samples ($n = 7$) drawn from a peripheral vein 3 min after intubation, skin incision, sternal splitting, sternal retraction, 15 and 30 min after sternotomy and, finally, in the recovery room (table I).

All specimens for vasopressin assay were collected into precooled heparinized plastic tubes and the separated plasma was stored at 20 °C before the measurement of the vasopressin concentration by immunoassay.

Since vasopressin is not metabolized in the lungs (Lansome, 1974) it was believed reasonable to compare venous and arterial samples. No correction was made for haemodilution on bypass because it is probably the concentration at the end organ that is important rather than the total amount of hormone released.

RESULTS

The pattern of the changes in heart rate and arterial pressure during the coronary artery operations ($n = 14$) (table I) were as would be predicted from clinical experience. Mean heart rate for the group increased by 20 beat min^{-1} on intubation despite beta-adrenoceptor blockade, decreased thereafter to an intermediate value, but increased significantly again in the postoperative period. Arterial pressure increased during the splitting of the sternum, decreased significantly during retraction of the pericardium and was increased in the postoperative period, when 11 of the 14 patients (79%) required nitroprusside to control hypertension. Both arterial and central venous pressures decreased abruptly on the institution of cardiopulmonary bypass.

Patients undergoing thymectomy (who were not in receipt of beta-adrenoceptor blocking drugs) had more stable heart rates and arterial pressures with similar but less marked changes on intubation and sternotomy.

Plasma sodium concentration and osmolality (table II) were constant. The cardiac patients produced copious volumes of urine without mannitol or diuretics, in spite of high circulating concentrations of vasopressin.

Plasma vasopressin concentrations are presented in a semilogarithmic plot in figures 1 and 2. In the coronary artery bypass patients, the median increased significantly from an initial value of 1.2 to 5.6 pmol litre^{-1} after intubation. It increased more markedly on sternotomy to reach a peak of 48 pmol litre^{-1} after retraction of the pericardium. Thereafter, the tendency for the vasopressin concentration to decrease was reversed after the initiation of cardiopulmonary bypass, when the maximum values were achieved in all patients, with a median value of 123 pmol litre^{-1}—a 100-fold increase over the preinduction values. Concentrations remained increased (34 pmol litre^{-1}) in the postoperative period.

Inspection of the vasopressin data from the patients undergoing thymectomy indicates that the stimulus of sternotomy produced a vasopressin response which was similar to that observed in the cardiac surgery group (24 and 30 pmol litre^{-1}), while comparison of the two plots suggests that the release of vasopressin in response to pericardial traction and to CPB was superimposed upon this.

DISCUSSION

Stimuli which provoke the release of vasopressin include hypotension (aterial and venous), pain and "surgical stress", decreases in plasma osmolality, and other less well evaluated factors such as morphine and hypoxia. In this study the most marked changes in vasopressin concentration were clearly related to haemodynamic factors.

TABLE II. *Mean plasma and urine composition (SEM) before and after coronary artery surgery and thymectomy*

	Before op.	During CPB	After op.
Coronary artery graft			
Plasma osmolality (mosm litre^{-1})	282 (1.5)	285 (1.1)	284 (1.9)
Plasma sodium (mmol litre^{-1})	136 (0.9)	137 (0.9)	135 (1.5)
Urine flow (ml h^{-1})	77 (14.8)	139 (30.4)	176 (47.8)
Urine osmolality (mosm litre^{-1})	527 (60)	492 (58)	390 (22)
Thymectomy			
Plasma osmolality (mosm litre^{-1})	280 (4.0)		280 (8.1)

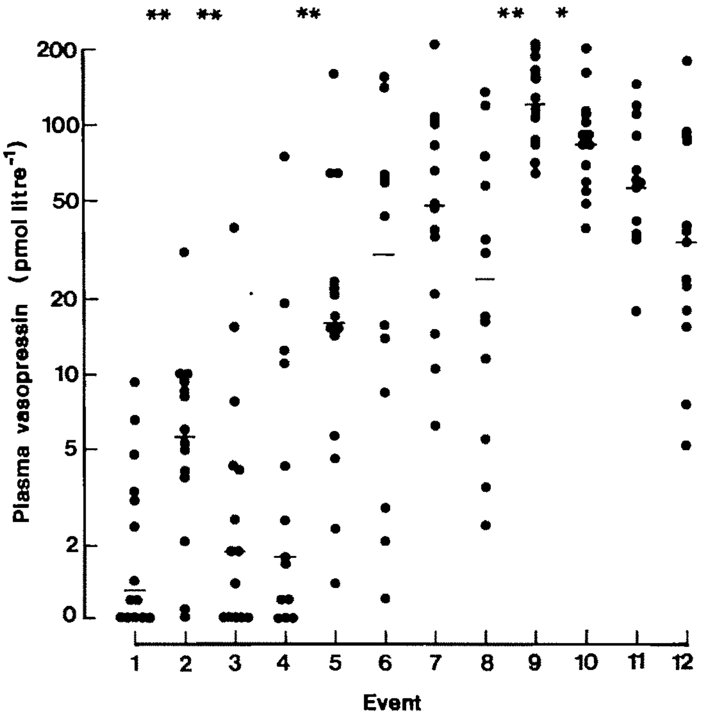

FIG. 1. Plasma vasopressin concentrations during coronary artery surgery, plotted logarithmically. The numbers refer to the events listed in table I. Statistical significance of the changes: $*P < 0.05$; $**P < 0.01$.

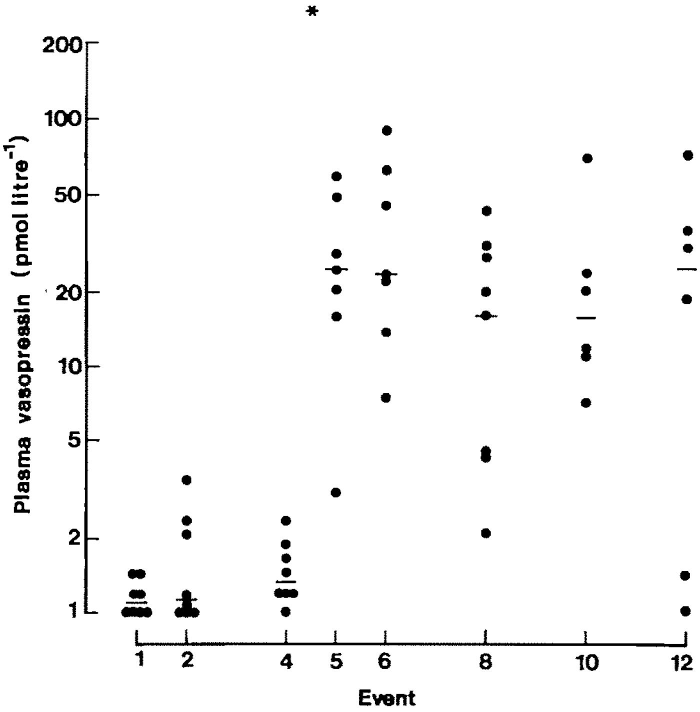

FIG. 2. Plasma vasopressin, plotted logarithmically, during thymectomy. The numbers refer to the events listed in table I. Statistical significance of the changes: $*P < 0.05$.

The abrupt decreases in arterial and right atrial pressures on the institution of bypass (table I) were associated with the highest concentrations of vasopressin, values which were more than seven times those at the nearest equivalent stage during thymectomy. Since the effects of atrial emptying and arterial hypotension (Forsling, 1982) on vasopressin release are well established, we must conclude that such mechanisms explain our findings, although the very high concentrations of vasopressin attained are greater than those previously demonstrated to be caused by circulatory effects in man. However, this observation may indicate the severity of the circulatory changes which occur in the course of cardiopulmonary bypass.

Apart from sensitivity to mean pressure, baroreceptors also respond to pulse pressure. There is some evidence (Levine et al., 1981) that the increase in vasopressin concentration is attentuated by the use of pulsatile bypass (our routine practice), although other work (Frater et al., 1980) suggests that this effect is not significant.

The lesser, but still substantial, increase in vasopressin concentration on sternotomy, which was similar in the two groups, remains to be explained. One simple explanation would be that the pain of sawing the sternum is the trigger stimulus and, indeed, in patients undergoing thymectomy who did not receive beta-adrenoceptor blocking agents, the mean heart rate increased from 65 beat min^{-1} (SEM 3.5) to 72 beat min^{-1} (SEM 4.8), suggesting activation of the sympathetic nervous system. At the same time, intrathoracic venous pressure (table I) tended to decrease as the sternum was split, and we postulate that this may at least be a contributory factor.

The plasma osmolality and sodium concentration do not change during or after bypass and, therefore, can have no influence on the release of vasopressin (table II). The vasopressin concentrations were considerably greater than those which normally produce maximal antidiuresis. It is interesting to speculate, therefore, why such large volumes of urine were produced after cardiac surgery in the absence of diuretic therapy. Although it may be attributable to the solute load, which was equivalent to 2500 ml of isotonic electrolyte solution, there must be some other factor which acts on the kidney to reduce the response to vasopressin. Possible contributing factors are the effects of intraoperative cooling on renal medullary gradients and the direct effect of vasopressin on the renal microcirculation. On the other hand, it has been shown that cooling does not influence the release of vasopressin from the pituitary (Thomson, Thompson and Forsling, 1980).

Hypoxia, a known cause of vasopressin release (Forsling and Aziz, 1983) can be excluded as a possible aetiological factor in producing the increases in plasma vasopressin concentration because oxygenation was well maintained during bypass and in the postoperative period. Morphine has been reported both to stimulate (Lightman and Forsling, 1980) and to inhibit (Woods et al., 1983) the release of vasopressin. In view of the large doses (1 mg kg^{-1}) give to the cardiac patients, it is not possible to exclude some influence, but it cannot be responsible for the short-term responses seen. Therefore, it seems likely that vasopressin was released, in both groups, in response to hypotensive and hypovolaemic haemodynamic changes.

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EVOKED ELECTROMYOGRAPHIC AND MECHANICAL RESPONSES OF THE ADDUCTOR POLLICIS COMPARED DURING THE ONSET OF NEUROMUSCULAR BLOCKADE BY ATRACURIUM OR ALCURONIUM, AND DURING ANTAGONISM BY NEOSTIGMINE

N. J. N. HARPER, E. G. BRADSHAW AND T. E. J. HEALY

SUMMARY

The effects of atracurium and alcuronium on the evoked mechanical and electromyographic responses of the adductor pollicis were investigated in 30 adult patients. The ulnar nerve was stimulated with trains of four supramaximal pulses of 0.2 ms duration and a frequency of 2 Hz at intervals of 20 s. The mechanical response was measured using a strain gauge force transducer and the evoked compound action potential (ECAP) was recorded simultaneously using a Medelec MS91 electromyography system. Depression of the electromyographic and mechanical responses, caused by atracurium, was similar during onset and antagonism of blockade. During onset of blockade by alcuronium, the mechanical response was depressed to a significantly greater extent compared with the ECAP. This difference was not observed during antagonism with neostigmine. The rates of onset of atracurium and alcuronium were generally similar, but the rate of onset of mechanical fade was greater in the alcuronium group. There was no significant quantitative difference between the rates of antagonism of alcuronium and atracurium when assessed by the mechanical first response ratio. Electromyographic first response and electromyographic and mechanical train-of-four ratios recovered more rapidly in the atracurium group. These findings suggest that the differences between mechanical and electromyographic measurements of neuromuscular blockade are drug-specific and are more pronounced during the onset of blockade than during its antagonism by neostigmine.

Assessment of neuromuscular blockade during anaesthesia, by the observation of the mechanical response of the adductor pollicis to stimulation of the ulnar nerve is widely accepted. As an alternative, the electrical activity of the muscle may be recorded (Churchill-Davidson and Christie, 1959). Most of the published work describing the effects of neuromuscular blocking agents on neuromuscular transmission in man has been based on measurement of the force of contraction of the adductor pollicis. In particular, this has applied to studies in which clinical assessment of recovery has been compared with the evoked response of the adductor pollicis (Walts, Levin and Dillon, 1970; Ali and Kitz, 1973; Ali et al., 1975; Brand et al., 1977). Early studies suggested that the mechanical and electromyographic responses were equally affected by neuromuscular blocking agents (Ali, Utting and Gray, 1970, 1971). However, other workers have demonstrated that the reduction in the mechanical response was greater than that of the evoked compound action potential (ECAP) during the onset of action of tubocurarine (Katz, 1973; Epstein and Epstein, 1973) and this phenomenon has also been observed during recovery from blockade (Katz, 1973). Suxamethonium appears to have the opposite effect in that the mechanical response is depressed to a lesser extent than the ECAP (Katz, 1973; Shanks and Jarvis, 1980). Shanks and colleagues (1981) reported that, unexpectedly,

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N. J. N. HARPER, M.B., CH.B., F.F.A.R.C.S.; E. G. BRADSHAW, M.D., F.F.A.R.C.S.; T. E. J. HEALY, M.SC., M.D., F.F.A.R.C.S.; Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.
Correspondence to N. J. N. H.

alcuronium resembles suxamethonium in this respect. The relative effects of atracurium on the ECAP and the mechanical response of the adductor pollicis have not been previously reported.

The present study was undertaken to compare the evoked mechanical and electromyographic responses of the adductor pollicis during the onset of neuromuscular blockade by alcuronium or atracurium, and during the antagonism of residual blockade by neostigmine.

PATIENTS AND METHODS

Thirty adult patients (ASA physical status I or II) gave consent to the investigations, which had been approved by the hospital Ethics Committee. The patients, who were free from any neuromuscular disorder, were to undergo ophthalmic or minor orthopaedic surgery. Sixteen patients received alcuronium and 14 received atracurium. The patients were premedicated with pethidine 25–50 mg and promethazine 25 mg 1 h before surgery. Anaesthesia was induced with thiopentone until the eyelash reflex was abolished, and maintained with 67% nitrous oxide in oxygen supplemented with fentanyl 0.1–0.2 mg. No halogenated inhalation agent was given. In some patients, additional small increments of thiopentone (up to a total of 10 mg kg^{-1}) were given to prevent movement while the control responses were recorded. Alcuronium 0.2–0.3 mg kg^{-1} or atracurium 0.4 mg kg^{-1} was administered i.v. and tracheal intubation was performed after spraying the larynx with 10% lignocaine. Controlled ventilation was adjusted to maintain normocapnia (Gould Mk IV Capnometer).

The ulnar nerve was stimulated supramaximally at the left wrist using silver–silver chloride surface electrodes. Trains-of-four square wave pulses of 0.2 ms duration at a frequency of 2 Hz were repeated at 20-s intervals using a modified portable electromyography system (Medelec MS91). The mechanical and electromyographic responses of the adductor pollicis were recorded simultaneously. The amplitude of the contraction responses and the amplitude of the electromyographic responses were compared during the onset of neuromuscular blockade and the subsequent antagonism of residual blockade. The indices used were the train of four ratio (T4:T1) and the ratio of the first response to the mean of three control (pre-relaxant) values (T1:T0). When the T1:T0 ratio had recovered spontaneously to 0.2, atropine 14 µg kg^{-1} and neostigmine 35.7 µg kg^{-1} were given i.v. over 10 s. Subsequently, the ECAP and the mechanical responses were monitored for at least 10 min.

Mechanical response

The force of contraction of the adductor pollicis was measured using a transducer incorporating two pairs of strain gauges (Bradshaw and Maddison, 1979) and was displayed on a chart recorder (Ormed MX212) with a paper speed of 1 mm s^{-1}.

Electromyographic response

Silver–silver chloride surface recording electrodes were positioned over the motor point of the adductor pollicis and ventrally over the head of the second metacarpal. An earth electrode was

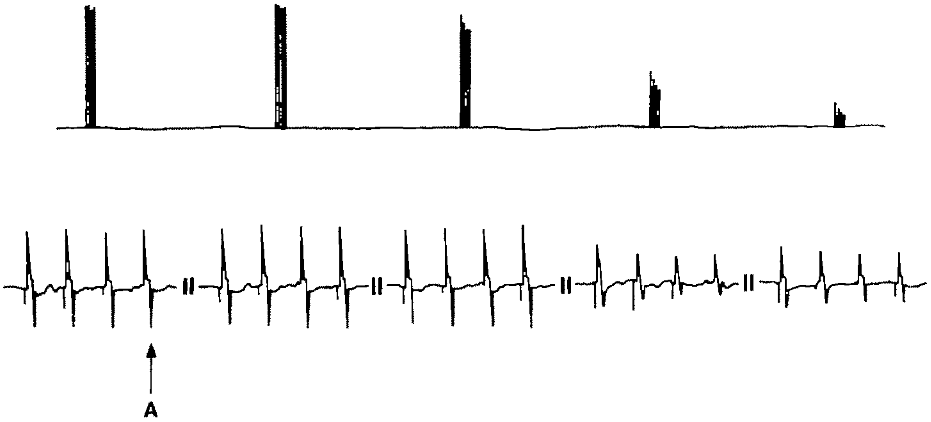

FIG. 1. Typical recordings of the simultaneous mechanical and electromyographic responses of the adductor pollicis following the administration of alcuronium. The EMG trace was recorded at a slower paper speed via a digital buffer (Medelec MS 91).

TABLE I. *Onset of blockade after alcuronium or atracurium measured by mean first response ratio (T1 : T0) (SEM).* *P < *0.05;* **P < *0.01*

	Time after administration (min)			
	1	2	3	4
Alcuronium				
ECAP	0.92 (0.03)	0.47 (0.07)	0.35 (0.07)	0.16 (0.07)
Mechanical	0.8 (0.05)	0.26 (0.06)	0.13 (0.03)	0.04 (0.02)
Difference	0.12**	0.21**	0.22**	0.12*
Atracurium				
ECAP	0.96 (0.02)	0.53 (0.06)	0.14 (0.03)	0.06 (0.02)
Mechanical	0.94 (0.05)	0.44 (0.08)	0.16 (0.04)	0.08 (0.02)
Difference	0.02	0.09	−0.02	−0.02

placed on the dorsal aspect of the hand. The ECAP was filtered, amplified and recorded using the Medelec system. In addition to the oscilloscope display, a permanent record was obtained by conversion of the signal to digital form. A reconstituted analogue waveform was recorded at slow speed on heat-sensitive paper and the amplitude of the total deflection was measured.

Results was evaluated using a paired or unpaired Student's *t* test as appropriate.

RESULTS

Typical recordings of the force of contractions and the corresponding ECAP of the adductor pollicis are shown in figure 1.

Onset of blockade

The mean ratios of the first response of the train to the control (T1 : T0) as blockade progressed are shown in table I. In the patients who received alcuronium, the mechanical response was depressed to a significantly greater extent than the ECAP at each time interval. This difference was not seen in those patients who received atracurium. Scattergrams of the T1:T0 ratios for force and ECAP measurements for all patients at 1, 2 and 3 min are shown in figures 2 and 3. There was an approximately linear relation in the atracurium group. In the alcuronium group, however, the data suggest that the magnitude of the disparity between the two methods of measurement depends on the degree of blockade, and regression analysis may be inappropriate. The corresponding train-of-four ratios are shown in table II. The degree of fade in the alcuronium group was significantly greater (paired *t* test) when measured mechanically. In the atracurium group the difference between the two methods of measurement was not significant.

Rate of onset

First response ratio (T1 : T0). There was no significant difference in the degree of blockade measured mechanically or electromyographically, at each time interval up to 4 min after the administration of either alcuronium or atracurium.

Train-of-four ratio (T4 : T1). The degree of fade of the mechanical response was greater in the alcuronium group than in the atracurium group ($P < 0.01$, unpaired *t* test) at 1 and 2 min after administration of the myoneural blocking drug.

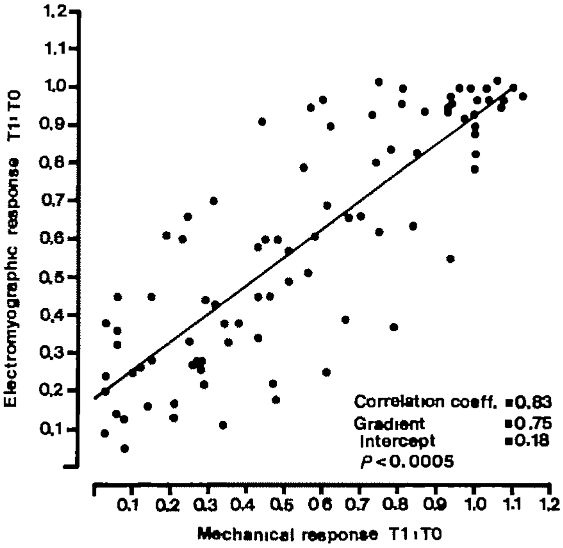

FIG. 2. Mechanical and electromyographic first response ratios (T1:T0) at 1, 2 and 3 min after the administration of atracurium.

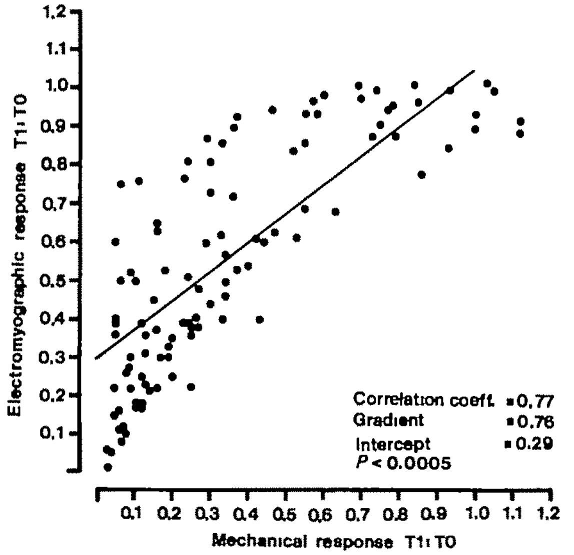

FIG. 3. Mechanical and electromyographic first response ratios (T1:T0) at 1, 2 and 3 min after the administration of alcuronium.

There was no significant difference in ECAP fade between the two groups.

Antagonism of blockade

First response ratio (T1 : T0). There was no significant difference (paired *t* test) between mechanical and ECAP estimations of blockade at any time up to 10 min after administration of neostigmine to either group of patients (table III).

Train of Four Ratio (T4 : T1). The corresponding train-of-four ratios are shown in table IV. In the alcuronium group there was no significant difference between the methods of measurement. In the atracurium group there was a trend towards a greater degree of fade of the mechanical response than of the ECAP. This reached significance only at 8 min (paired *t* test), at which time antagonism was almost complete.

Rate of antagonism

First response ratio (T1 : T0). The degree of antagonism of blockade was greater at each time interval in the atracurium group compared with the alcuronium group when measured electromyographically ($P < 0.05$, unpaired *t* test). The difference between the two groups was greatest between 4 and 7 min ($P < 0.01$). There was no significant difference between the rates of first response antagonism of atracurium and alcuronium when measured mechanically (unpaired *t* test) (table III).

TABLE II. *Onset of blockade measured by mean train-of-four ratio (T4 : T1) (SEM).* *$P < 0.05$; **$P < 0.01$

	Time after administration (min)			
	1	2	3	4
Alcuronium				
ECAP	0.94 (0.02)	0.56 (0.05)	0.41 (0.05)	0.16 (0.06)
Mechanical	0.85 (0.02)	0.44 (0.05)	0.27 (0.04)	0.05 (0.03)
Difference	0.09**	0.12**	0.14*	0.11**
Atracurium				
ECAP	0.99 (0.01)	0.66 (0.02)	0.5 (0.07)	0.21 (0.07)
Mechanical	0.94 (0.003)	0.66 (0.05)	0.36 (0.07)	0.26 (0.07)
Difference	0.05	0.00	0.14	−0.05

TABLE III. *Antagonism of blockade measured by mean first response ratio (T1 : T0) (SEM)*

	Time after administration of neostigmine (min)					
	0	2	4	6	8	10
Alcuronium						
ECAP	0.19 (0.04)	0.34 (0.06)	0.54 (0.06)	0.66 (0.07)	0.74 (0.07)	0.79 (0.07)
Mechanical	0.17 (0.02)	0.37 (0.06)	0.62 (0.07)	0.79 (0.08)	0.88 (0.07)	0.93 (0.07)
Difference	0.02	−0.03	−0.08	−0.13	−0.14	−0.14
Atracurium						
ECAP	0.26 (0.03)	0.56 (0.05)	0.89 (0.02)	0.93 (0.02)	0.93 (0.02)	0.95 (0.02)
Mechanical	0.20 (0.02)	0.47 (0.04)	0.77 (0.05)	0.86 (0.06)	0.98 (0.05)	1.0 (0.06)
Difference	0.06	0.09	0.12	0.07	−0.05	−0.05

TABLE IV. *Antagonism of blockade measured by train-of-four ratio (T4 : T1) (SEM)* $^{**}P < 0.01$

	Time after administration of neostigmine (min)					
	0	2	4	6	8	10
Alcuronium						
ECAP	0.21 (0.04)	0.22 (0.03)	0.32 (0.05)	0.43 (0.07)	0.5 (0.05)	0.58 (0.04)
Mechanical	0.1 (0.04)	0.19 (0.04)	0.33 (0.03)	0.42 (0.03)	0.49 (0.03)	0.54 (0.03)
Difference	0.11	0.03	−0.01	0.01	0.01	0.04
Atracurium						
ECAP	0.21 (0.06)	0.36 (0.07)	0.71 (0.06)	0.87 (0.04)	0.97 (0.03)	0.97 (0.02)
Mechanical	0.08 (0.02)	0.34 (0.04)	0.64 (0.03)	0.82 (0.04)	0.86 (0.02)	0.89 (0.02)
Difference	0.13	0.02	0.07	0.05	0.11**	0.08

Train-of-four ratio (T4 : T1). Compared with the alcuronium group, the T4:T1 ratio in the atracurium group was significantly greater at each time interval after the administration of neostigmine ($P < 0.01$, unpaired t test). The rate of T4: T1 recovery of atracurium was greater whether measured mechanically or electromyographically.

DISCUSSION

Neuromuscular blockade during anaesthesia is usually monitored by recording the force of contraction of the muscles of the hand in response to stimulation of the ulnar nerve at the elbow or wrist. This technique requires isometric conditions and the application of a constant preload to the muscle in order to ensure constant initial muscle fibre length. The term force–displacement transducer is therefore inappropriate. It may be difficult, because the muscles of the hand are complex, to measure the force of contraction of a single muscle in isolation in the direction of its application. Transducers which are arranged in a pistol grip configuration may measure a vector of the force of contraction of the flexor pollicis brevis in addition to the adductor pollicis. An additional source of error may result from inadequate fixation of the transducer in relation to the second metacarpal, from which the two heads of the adductor pollicis originate. Variations in preload and base line drift may result.

Despite these limitations, most of our knowledge of the relation between evoked neuromuscular responses and the clinical criteria for recovery from neuromuscular blockade is based on the measurement of force of contraction of the adductor pollicis (Walts, Levin and Dillon, 1970; Ali and Kitz, 1973; Ali et al., 1975; Brand et al., 1977).

Measurement of the evoked compound action potential (ECAP) using surface electrodes has several advantages over mechanical techniques. First, the response does not depend on mechanical fixation of the muscle because maintenance of preload is unnecessary. Second, many more muscle groups are accessible for study. These include the muscles of the hypothenar eminence, the small muscles of the hand and the muscles supplied by the facial nerve and the common peroneal nerve. Third, the electromyographic response reflects only those factors which influence neuromuscular transmission. Therefore, the ECAP is largely independent of factors which influence contractility, including the major effects of hydrocarbon inhalation agents and changes in arterial carbon dioxide tension (Katz, 1965). These factors must be standardized in an investigation of the relation between mechanical and electromyographic evoked responses.

There are several methods used for the analysis of the ECAP. These include measurement of the amplitude of the major deflection from the isoelectric line (fig. 4A), the sum of the amplitudes of the major positive and negative deflections (fig. 4B) and the area contained within the rectified waveform (fig. 4C). The effect of neuromuscular blocking drugs on these indices is usually assumed to be equivalent. Pugh, Kay and Healy (1984) have demonstrated a near linear correlation between the depression of the major potential and that of the integrated signal during onset of non-depolarizing neuromuscular blockade. It is reasonable to assume, therefore, that our findings may also describe the relation between the mechanical response and that measured by a monitor utilizing the integrated electromyogram.

The relation between the depression of the evoked mechanical and electrical responses of the

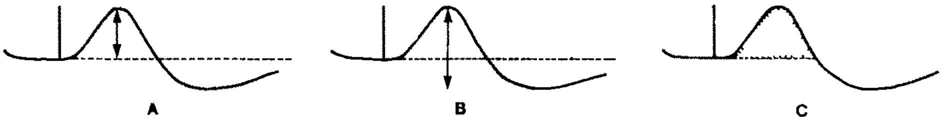

FIG. 4. Three methods of evaluation of the evoked compound action potential: A Amplitude of the negative deflection; B total amplitudes of the negative and positive deflections; C area contained within the rectified waveform (integration).

adductor pollicis induced by tubocurarine has been examined by several workers (Katz, 1965, 1973; Epstein and Epstein, 1973). There is general agreement that the mechanical response to a single stimulus is depressed to a greater extent than the evoked electromyogram. This phenomenon may vary quantitatively between neuromuscular blocking agents, and the opposite relation has been demonstrated during blockade by suxamethonium (Shanks and Jarvis, 1980; Donati and Bevan, 1984) and alcuronium (Shanks et al., 1981).

In the present study we were unable to demonstrate a significant difference between the mechanical and ECAP responses to atracurium, with the exception of the train-of-four ratio at a time when recovery was almost complete (table IV). In contrast with the work of Shanks and colleagues (1981), we found that alcuronium depressed the mechanical response to a significantly greater degree than the ECAP during the onset of blockade. This difference was observed in both first response (table I) and train-of-four (table II) ratios. Therefore, we suggest that alcuronium may be grouped with tubocurarine, and that atracurium may be placed in an intermediate position between other non-depolarizing blockers and suxamethonium, in terms of their relative effects on the mechanical response and the ECAP.

The disparity between our results and those of Shanks and colleagues (1981) with respect to alcuronium may be partially explained by differences in methodology. In their study, electrodes were placed over the first dorsal interspace of the hand and, therefore, predominantly reflected the electrical activity of the first dorsal interosseus muscle. They compared the ECAP with the force produced by adduction of the thumb in response to ulnar nerve stimulation and were able to demonstrate that the mechanical response ED_{50} was significantly greater than that obtained electromyographically.

It is probable that there is variation in the sensitivity of the different muscles of the hand to neuromuscular blocking drugs. Katz (1973) has demonstrated that the ECAP response of the adductor pollicis is depressed by tubocurarine to a greater extent than that of the hypothenar muscles. Clinical observation suggests that this relationship is also applicable to the force of contraction of the two muscle groups. A disparity in the opposite direction between the relative sensitivity of the adductor pollicis and the first dorsal interosseus muscle may reconcile the findings of Shanks and colleagues (1981) with those of the present study. In addition, an unusually long pulse duration of 0.1–0.15 s was used. This may have produced repetitive firing of motor units, leading to enhancement of the force of contraction of the adductor pollicis, without increasing the amplitude of the ECAP (Epstein et al., 1969).

The rate of onset of atracurium was not significantly different from that of alcuronium when the ECAP was considered. The rate of onset of mechanical first twitch depression (T1:T0) was similar in both groups. However, the onset of mechanical fade (T4:T1) was more rapid in the first 2 min after atracurium. Studies in which the rate of onset of clinically apparent non-depolarizing blockade has been measured were restricted to the first response ratio (T1:T0) (Foldes et al., 1983; Gergis et al., 1983; Ali et al., 1984; Bencini and Newton, 1984). It is, therefore, impossible to predict whether the accelerated onset of T4:T1 fade after atracurium will be reflected in the more rapid development of apnoea and satisfactory intubating conditions. It has been postulated that the relative rate of onset of T4:T1 fade and T1:T0 depression may depend on the accessibility of prejunctional and postjunctional receptors, respectively (Calvey et al., 1983). The intrajunctional nature of this phenomenon suggests that the relation between single response depression and fade will be reflected equally in the compound action potential and the force of muscle contraction. However, our findings demonstrate that the onset of mechanical fade after atracurium is more rapid than that of the ECAP, whilst there is no significant difference between the rates of onset of first twitch depression. This suggests that the ratio of fade to single response depression (T4:T1 divided by T1:T0) is dependent upon the method of measurement in addition to the relative preponderance of prejunctional and postjunctional receptor occupancy. Therefore, caution should be exercised when comparing electromyographic and force measurements and their possible relation to the sites of action of neuromuscular blocking drugs.

The difference between the mechanical and electromyographic responses to alcuronium observed during onset was not seen during antagonism of residual blockade by neostigmine. Although neostigmine has a nicotinic agonist effect at the neuromuscular junction (Hobbiger, 1950), it is probable that this will be reflected in an increase in both the ECAP and mechanical response. It is unlikely that neostigmine in clinically applicable doses will affect contractility sufficiently to enhance the mechanical response to a value similar to that of the electromyographic response.

In conclusion, we have demonstrated that, during the onset of blockade by alcuronium, the mechanical response of the adductor pollicis was depressed to a greater extent than the electromyographic response. The disparity between methods of measurement is not seen during the onset of atracurium-induced blockade or during antagonism of either drug by neostigmine. These findings suggest that studies of the antagonism of neuromuscular blockade by atracurium or alcuronium may produce comparable results, but caution is necessary in comparing electromyographic and mechanical measurements during the onset of blockade by alcuronium.

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ANTAGONISM OF PROFOUND NEUROMUSCULAR BLOCKADE INDUCED BY VECURONIUM* OR ATRACURIUM

Comparison of Neostigmine with Edrophonium

J. E. CALDWELL, E. N. ROBERTSON AND W. L. M. BAIRD

SUMMARY

The effectiveness of neostigmine 0.07 mg kg^{-1} and edrophonium 0.8 mg kg^{-1} as antagonists of profound neuromuscular blockade induced by vecuronium 0.1 mg kg^{-1} or atracurium 0.5 mg kg^{-1} was studied in 59 healthy patients. The antagonists were administered 5 min after total ablation of the twitch response and the end-point of recovery was a train-of-four ratio of 70%. In 30 patients given vecuronium the mean time to reach this point (duration TOF$_{70}$) was 66.7 min in the control group (no antagonist), 43.5 min in the group given neostigmine and 59.8 min in the group given edrophonium. The duration TOF$_{70}$ was shorter in the neostigmine group than in the control ($P < 0.01$) and edrophonium ($P < 0.01$) groups. The duration TOF$_{70}$ did not differ from control in the edrophonium group. In 29 patients given atracurium, the durations TOF$_{70}$ were 66.4, 44.1 and 54.9 min in the control, neostigmine and edrophonium groups, respectively. The durations TOF$_{70}$ in the neostigmine ($P < 0.01$) and edrophonium ($P < 0.01$), groups were shorter than control. The duration TOF$_{70}$ of the neostigmine group was shorter than in the edrophonium group ($P < 0.01$). These results show that profound neuromuscular blockade cannot be rapidly antagonized by either of these two agents, but if reversal is required under these circumstances, neostigmine would be the more effective drug.

In recent years interest has revived in the use of edrophonium as an antagonist of non-depolarizing neuromuscular blockade. Adequate and sustained antagonism of pancuronium- or tubocurarine-induced neuromuscular blockade can be achieved with large doses of edrophonium (Bevan, 1979; Kopman, 1979; Ferguson, Egerszegi and Bevan, 1980; Morris et al., 1981). Subsequently, Cronnelly, Morris and Miller (1982) demonstrated that, when antagonizing tubocurarine-induced blockade stabilized at 90% depression of twitch height, edrophonium 0.5 mg kg^{-1} was equipotent with neostigmine 0.043 mg kg^{-1}. At that dose the onset of action of edrophonium was more rapid, the antagonism was sustained and the duration of action was only slighly shorter than that of neostigmine. Edrophonium 0.5–1.0 mg kg^{-1} has been shown to be a reliable antagonist of blockades induced by vecuronium (Foldes et al., 1981; Baird, Bowman and Kerr, 1982) and by atracurium (Baird and Kerr, 1983; Jones, Pearce and Williams, 1984). It is important to note, however, that in all these studies the edrophonium was administered only when there was some demonstrable spontaneous recovery of neuromuscular transmission. In the present study equipotent doses of neostigmine and edrophonium were administered during profound, unquantifiable neuromuscular blockade, induced by vecuronium or atracurium, and their effectiveness as antagonists was compared.

PATIENTS AND METHODS

Fifty-nine healthy patients gave informed consent to their inclusion in this study, which was approved by the Ethics Committee. Approximately

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J. E. CALDWELL, M.B. CH.B., D.R.C.O.G., F.F.A.R.C.S.; E. N. ROBERTSON, B.SC., M.B. CH.B., F.F.A.R.C.S.; W. L. M. BAIRD, M.B. CH.B., D.A., F.F.A.R.C.S., M.R.C.P. (GLASG.); Department of Anaesthesia, Royal Infirmary, Glasgow, G31 3ER.

Correspondence to E.N.R.

* The initial results from the vecuronium group were presented at the 4th Ludwig Boltzmann Symposium, Vienna, 1984.

1 h after premedication with papaveretum 10–20 mg plus hyoscine 0.2–0.4 mg i.m., anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and was maintained thereafter with 67% nitrous oxide in oxygen plus 1% halothane (inspired). The Myograph 2000 neuromuscular transmission analyser (Biometer, Denmark) was used to deliver supramaximal stimuli of 0.2 ms duration at a frequencey of 0.1 Hz to the ulnar nerve via subcutaneous needle electrodes placed at the wrist, and to transduce and record the resulting evoked responses of the adductor pollicis muscle. Before the administration of the neuromuscular blocking drug, control responses to single twitch (0.1 Hz) and train-of-four (TOF) stimulation were recorded for at least 10 min, to allow stabilization.

The first 30 patients received vecuronium 0.1 mg kg^{-1} i.v. Tracheal intubation was performed when 100% depression of twitch height was achieved, and IPPV was instituted. Five minutes after total ablation of the single twitch response, the patients were allocated randomly to one of three groups: group 1 (control) received no antagonist; group 2 received neostigmine 0.07 mg kg^{-1} plus atropine 1.2 mg i.v.; group 3 received edrophonium 0.8 mg kg^{-1} plus atropine 1.2 mg i.v. When twitch height had returned to control the stimulation mode was changed to TOF and monitoring was continued until the TOF ratio was 70%.

All times were measured from the end of injection of the neuromuscular blocking drug. Indices recorded were: onset (time to 100%

TABLE I. *Physical characteristics of patients in the study (mean ± SEM).* *$P < 0.01$, *1 v. 2 and 3*

	Group 1 (control)	Group 2 (neostigmine)	Group 3 (edrophonium)
Age (yr)			
Vecuronium	35.0±2.9* (n = 10)	55.7±3.6* (n = 10)	49.0±5.7* (n = 10)
Atracurium	43.6±3.6 (n = 10)	38.1±4.6 (n = 9)	36.1±2.8 (n = 10)
Weight (kg)			
Vecuronium	68.2±3.4 (n = 10)	67.2±2.6 (n = 10)	66.3±3.1 (n = 10)
Atracurium	65.8±1.9 (n = 10)	61.4±3.3 (n = 9)	68.1±5.1 (n = 10)

TABLE II. *Indices of recovery (min) (mean ± SEM) for the patients who received vecuronium 0.1 mg kg^{-1}. Controls received no antagonist, the others received neostigmine 0.07 mg kg^{-1} or edrophonium 0.8 mg kg^{-1} i.v. 5 min after total ablation of the twitch response. All times were measured from the end of injection of vecuronium. Duration 5 = time to twitch height 5% of control; duration 25 = time to twitch height 25% of control; recovery index = time from 25% to 75%; duration 95 = time to twitch height 95% of control; duration TOF_{70} = time till train-of-four ratio 70%.* *$P < 0.05$; **$P < 0.01$

	Control (n = 10)	Neostigmine (n = 10)	Edrophonium (n = 10)
Duration 5	27.6±1.2	14.1±0.9	21.5±2.6
		*	
	**		**
Duration 25	34.6±1.5	20.1±1.9	29.8±2.8
		ns	
	**		**
Recovery index	11.6±0.9	9.9±1.6	10.6±1.2
		ns	
	ns		ns
Duration 95	51.7±2.9	35.9±4.3	48.0±4.3
		ns	
	**		**
Duration TOF_{70}	66.7±3.3	43.5±5.1	59.8±5.6
		ns	
	**		*

TABLE III. *Indices of recovery (min) (mean ± SEM) in the patients who received atracurium 0.5 mg kg^{-1}. All times were measured from the end of injection of atracurium. Controls received no antagonist, the others received neostigmine 0.07 mg kg^{-1}, or edrophonium 0.8 mg kg^{-1} i.v., 5 min after total ablation of the twitch response. Duration 5 = time to twitch height 5% of control; duration 25 = time to twitch height 25% of control; recovery index = time from 25% to 75%; duration 95 = time to twitch height 95% of control; duration TOF$_{70}$ = time to train-of-four ratio 70%. *F < 0.05; **P < 0.01*

<table>
<tr><th></th><th colspan="2">Control
(n = 10)</th><th colspan="2">Neostigmine
(n = 9)</th><th colspan="2">Edrophonium
(n = 10)</th></tr>
<tr><td>Duration 5</td><td colspan="2">33.2±2.3</td><td colspan="2">14.0±1.2</td><td colspan="2">20.6± 3.4</td></tr>
<tr><td></td><td colspan="6">**</td></tr>
<tr><td></td><td colspan="3">**</td><td colspan="3">*</td></tr>
<tr><td>Duration 25</td><td colspan="2">43.0±2.0</td><td colspan="2">22.1±1.8</td><td colspan="2">32.6±3.3</td></tr>
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<tr><td>Recovery index</td><td colspan="2">11.6±0.7</td><td colspan="2">11.8±0.7</td><td colspan="2">11.0±0.8</td></tr>
<tr><td></td><td colspan="6">ns</td></tr>
<tr><td></td><td colspan="3">ns</td><td colspan="3">ns</td></tr>
<tr><td>Duration 95</td><td colspan="2">59.4±2.0</td><td colspan="2">39.1±2.5</td><td colspan="2">49.2±3.8</td></tr>
<tr><td></td><td colspan="6">*</td></tr>
<tr><td></td><td colspan="3">**</td><td colspan="3">*</td></tr>
<tr><td>Duration TOF₇₀</td><td colspan="2">66.4±2.2</td><td colspan="2">44.1±2.9</td><td colspan="2">49.2±3.8</td></tr>
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depression of twitch height); durations 5, 25, 75 and 95 (times to 5, 25, 75 and 95% recovery of twitch height, respectively) and duration TOF$_{70}$ (time to a TOF ratio of 70%).

Subsequently, a further 29 patients were studied; neuromuscular blockade was induced with atracurium 0.5 mg kg^{-1} i.v. and an identical programme of study used.

Statistical analysis was by unpaired Student's *t* test. $P < 0.05$ was considered significant.

RESULTS

Physical characteristics of the patients are detailed in table I. The control patients who received vecuronium were younger than those in the neostigmine and edrophonium groups. Otherwise, the groups were comparable. There was no difference between the groups in the onset of neuromuscular blockade. Taking all the vecuronium patients, the mean onset time was 2.4 min (range 1.5–4.4 min). The equivalent time for the atracurium group was 2.4 min (1.3–5.9 min).

The indices of recovery in the patients who received vecuronium are shown in table II. The durations 5, 25, 95 and TOF$_{70}$ were shorter in the neostigmine group than in the edrophonium and control groups. The duration 5 of the edrophonium group was shorter than that in the control group.

The indices of recovery in the patients who received atracurium are shown in table III. The durations 5, 25, 95 and TOF$_{70}$ were shorter in the neostigmine group than in the edrophonium and control groups. The durations 5, 25, 95 and TOF$_{70}$ were shorter in the edrophonium group than in the control group.

Figure 1 demonstrates the recovery rates from 5% to 95% twitch height in each group. There

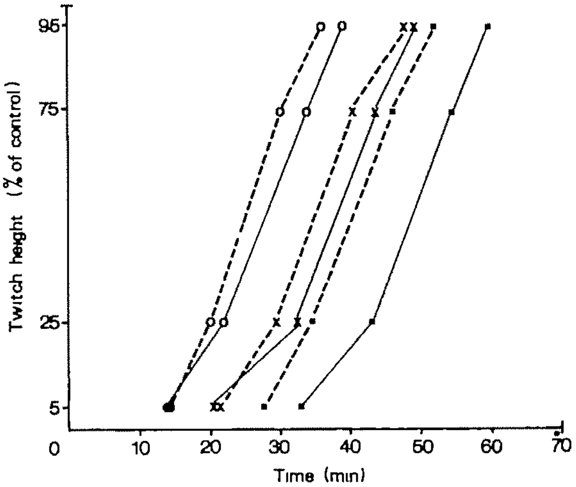

FIG. 1. Recovery of twitch height from 5% to 95% of control. Neuromuscular blocking drug administered: ---- = vecuronium, —— = atracurium. Antagonist administered: ○ = neostigmine, × = edrophonium, ■ = none (control).

were no differences between the groups in recovery index (time from 25% to 75% twitch height recovery).

DISCUSSION

In this study with halothane used to maintain anaesthesia, the mean durations TOF_{70} of the control groups, after intubating doses of vecuronium 0.1 mg kg^{-1} and atracurium 0.5 mg kg^{-1}, were 66.7 and 66.4 min, respectively. This suggests that, in these circumstances, it is probably necessary to antagonize residual neuromuscular blockade for up to 1 h after the injection of these doses of vecuronium and atracurium. The onset times for vecuronium and atracurium in this study were in agreement with previous reports (Gramstad, Lilleaasen and Minsaas, 1982; Robertson et al., 1983).

The effect of age on the potency of vecuronium was studied by d'Hollander and colleagues (1982). Patients aged younger than 40 yr were compared with patients aged between 40 and 60 yr and no difference in potency was demonstrated. It seems reasonable to conclude, therefore, that the age difference within the vecuronium group was not an important factor in the interpretation of our results.

Since the doses of neostigmine and edrophonium were equipotent (Cronnelly, Morris and Miller, 1982; Baird, Bowman and Kerr, 1982), the groups can be compared with each other. In this study, neostigmine reduced the duration of action of vecuronium and atracurium compared with control. In contrast, edrophonium had no effect on the duration of action of vecuronium, but it did reduce the duration of action of atracurium. Edrophonium was less effective than neostigmine against either of these neuromuscular blocking agents. Since edrophonium has been shown to have a faster onset of action than neostigmine (Morris et al., 1981), it might have been expected that the duration 5, being the first clear evidence of a returning twitch response, would have been shorter in the edrophonium group. In fact, mean duration 5 was shorter in patients receiving either vecuronium or atracurium after neostigmine (fig. 1).

When antagonizing stable 90% tubocurarine-induced neuromuscular blockade, the time to the peak effect of edrophonium was 0.8–2.0 min (Cronnelly, Morris and Miller, 1982), and to peak effect of neostigmine was 7–11 min (Miller et al., 1974). In the present study, the concentrations of vecuronium and atracurium at the neuromuscular junction, when the antagonists were exerting their peak effect, were unknown. The more rapid demonstrable effect of neostigmine, in this study, was perhaps simply the result of a greater degree of spontaneous recovery being present when the neostigmine has its peak effect.

It has been suggested that the administration of an anticholinesterase, when there is likely to be a high concentration of vecuronium or atracurium at the neuromuscular junction, might induce some degree of ion-channel occlusion and that blockade would be enhanced (Bowman, 1985). No evidence of such an effect was found in this study: compared with control, the duration of neuromuscular blockade was not prolonged following the administration of neostigmine or edrophonium. However, it is not possible to dismiss the possibility of ion-channel occlusion, since this might explain why neither anticholinesterase agent induced a rapid, satisfactory antagonism of neuromuscular blockade.

After the twitch height reached 25% of control, the rate of recovery was similar in all groups (fig. 1). Differences in the durations 95 and TOF_{70} merely reflected events in the early phase of recovery and were probably not the result of a continuing process of antagonism. Therefore, the effectiveness of neostigmine and edrophonium as antagonizing agents would appear to be more dependent on their initial effect than on their duration of action.

Recently, Rupp, McChristian and Miller (1984) investigated the antagonism of vecuronium-, pancuronium- and atracurium-induced neuromuscular blockade by neostigmine or edrophonium, administered when the twitch height was less than 10% of the control response. Their results demonstrated that both antagonists were equally effective against atracurium, but that edrophonium was less effective than neostigmine against vecuronium and pancuronium. Although, in the present study, edrophonium was less effective than neostigmine in antagonizing atracurium-induced blockade, the results of these other workers are generally confirmed. Vecuronium has a predominantly postjunctional action (Bowman, Gibb and Marshall, 1983), while edrophonium has a significant prejunctional effect (Blaber, 1972), which is proportionately greater than that of neostigmine (Donati, Ferguson and Bevan, 1983). Under the conditions of the present and previous studies (Rupp, McChristian and Miller, 1984), the mode of action of edrophonium may be poorly matched to the neuromuscular-blocking properties of vecuronium and this might account for the relative ineffectiveness of edrophonium against vecuronium.

Neither neostigmine nor edrophonium will rapidly antagonize profound neuromuscular blockade induced by vecuronium or atracurium. In the clinical situation, antagonism of profound blockade is sometimes attempted either deliberately, for example after failed tracheal intubation, or unwittingly when neuromuscular function is not monitored. However, of the two drugs, neostigmine appears to be the more effective if antagonism of profound neuromuscular blockade is to be attempted.

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ANTAGONISM OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE OR EDROPHONIUM

B. A. ASTLEY, R. HUGHES AND J. P. PAYNE

SUMMARY

Antagonism of atracurium-induced neuromuscular blockade by neostigmine or edrophonium has been studied using the tetanic (50 Hz) and train-of-four (2 Hz) or single twitch responses of the adductor pollicis muscle in 22 anaesthetized patients. A further nine patients not given an anticholinesterase acted as a control group. In two groups (six patients for each anticholinesterase) in whom antagonism was attempted at 95–98% blockade of the tetanic response, recovery of the tetanic response after two or three doses of edrophonium 0.75 mg kg^{-1} *i.v. was not statistically different from that in the control group; recovery after two doses of neostigmine 2.5 mg i.v. was significantly faster* ($P < 0.001$)*. Recovery of the single twitch response after antagonism with edrophonium, although longer than that with neostigmine* ($P < 0.01$)*, was significantly shorter than in the control group* ($P < 0.05$)*. When edrophonium is given at the commencement of recovery, the initial rapid antagonism of tetanic block is not sustained, whereas antagonism by neostigmine is more persistent and the recovery phase is significantly shortened. In a further two groups of patients* ($n = 5$) *given atracurium 0.3 mg* kg^{-1} *i.v., antagonism was not attempted until the peak height of the tetanic contraction had reached approximately 50% of the control value. It was found that recovery of the tetanic and train-of-four responses was significantly faster* ($P < 0.05$–0.001) *after antagonism with edrophonium 0.75 mg* kg^{-1} *i.v. than with neostigmine 2.5 mg i.v. (approx. 0.04 mg* kg^{-1}*). The train-of-four response recovered more slowly than did the tetanic response after both agents* ($P < 0.05$–0.01)*.*

It has been reported that edrophonium, in relatively large doses, induces a more rapid antagonism of the neuromuscular blockade produced by pancuronium (Bevan, 1979), atracurium (Baird and Kerr, 1983; Jones, Pearce and Williams, 1984) and alcuronium (Harper, Bradshaw and Healy, 1984) than does neostigmine. However, since effective recovery is related to the degree of blockade immediately before antagonism (Katz, 1967), the present study was undertaken to determine whether edrophonium produces a more rapid antagonism of the partial or complete neuromuscular blockade induced by atracurium than does neostigmine, and whether antagonism is equally persistent after either anticholinesterase.

PATIENTS AND METHODS

Studies were performed on 22 patients about to undergo urological surgery. Informed consent was obtained from all patients and the studies were approved by the Ethics Committee of the St Peter's Hospital, London. In addition, a further group of nine patients who were allowed to recover spontaneously from the effects of atracurium, and who had also given their informed consent, acted as a control group.

No premedication was given and anaesthesia was induced with thiopentone 500–600 mg i.v. In

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BEVERLEY A. ASTLEY†, M.B., B.S., F.F.A.R.C.S.; R. HUGHES*, B.SC., M.SC., PH.D.; J. P. PAYNE, M.B., F.F.A.R.C.S., D.A.; Research Department of Anaesthetics, Royal College of Surgeons of England, and St Peter's Hospital, London WC2.
Present addresses:

†Department of Anaesthetics, University College Hospital, London WC1.

*Clinical Investigation Department, Clinical and Applied Research Division, The Wellcome Research Laboratories, Beckenham, Kent.

TABLE I. *Antagonism of 95–98% atracurium-induced blockade with two or three doses of edrophonium 0.75 mg* kg^{-1} *i.v. and two doses of neostigmine 2.5 mg i.v. preceded by atropine 1.2 mg. Recovery times in a control group of patients not given an anticholinesterase are shown for comparison. Mean values ± SEM. Significant differences:* **$P < 0.01$; ***$P < 0.001$. *Edrophonium* v. *control for the tetanic response was not significant; for the twitch,* $P < 0.05$

	No. patients	Time to 95% recovery (min)	
		Tetanic response	Single twitch
Edrophonium	6	24.3 ± 1.6	13.6 ± 1.3
		***	**
Neostigmine	6	9.6 ± 0.4	7.8 ± 0.8
		***	***
Control	9	28.9 ± 2.3	22.6 ± 2.5

12 patients tracheal intubation was achieved during the administration of 2–4% halothane inspired concentration, without the use of a neuromuscular blocking agent. Anaesthesia was then maintained with 60–66% nitrous oxide and 0.5% halothane in oxygen. Ventilation was controlled. In a further 10 patients, the trachea was intubated after the administration of atracurium 0.3 mg kg^{-1} i.v. In all patients, recordings of the tetanic contraction of the adductor pollicis were obtained by stimulating the ulnar nerve supramaximally at the wrist every 12 s with tetanic bursts of 50 Hz for 1 s. Simultaneous recordings were obtained of either the responses of the adductor pollicis muscle to single twitch (in 12 patients) or train-of-four stimulation (in 10 patients) of the ulnar nerve. Arterial pressure was measured via an indwelling polyethylene cannula placed in a radial artery. The electrocardiogram was recorded from non-conventional chest leads.

The first 12 patients, who were given halothane, were divided into two groups of six. In both groups atracurium in the dose range 0.15–0.3 mg kg^{-1} i.v. was used to produce 100% blockade of the tetanic response. As soon as signs of recovery of the peak tetanic contraction appeared, the patients were pretreated with atropine 1.2 mg and blockade was antagonized, in one group with two doses of neostigmine 2.5 mg i.v. and in the other with two or three doses of edrophonium 0.75 mg kg^{-1} i.v. given at 2.5-min intervals. All drugs were administered through a cannula in a large forearm vein and were flushed into the circulation with a fast flowing infusion.

The remaining 10 patients were divided into two groups ($n = 5$), and atracurium 0.3 mg kg^{-1} i.v. was given to both groups before intubation. When recovery of the peak height of the tetanic contraction had reached approximately 50% of its initial value, all the patients were pretreated with atropine as before. In one group residual blockade was antagonized with neostigmine 2.5 mg i.v. (approx. 0.04 mg kg^{-1}); in the other, with edrophonium 0.75 mg kg^{-1} i.v.

The results were analysed statistically using paired and unpaired t tests on log-transformed data.

RESULTS

The results obtained when 95–98% blockade induced by atracurium was antagonized with neostigmine and edrophonium in the two groups of six patients are set out in table I. The mean recovery time of *the tetanic response* for those patients given neostigmine was significantly faster than that in the control group of patients in whom neuromuscular blockade was not antagonized. Recovery after edrophonium was not significantly different from control. In contrast, the mean recovery time of *the single twitch response* after antagonism with edrophonium, although longer than recovery with neostigmine, was significantly shorter than recovery in the control group of patients ($P < 0.05$). Examples of these responses are shown in figure 1, which illustrates tracings of the tetanic and single twitch contractions of the adductor pollicis muscle from two patients given atracurium 0.3 mg kg^{-1} and 0.2 mg kg^{-1}, respectively. Neostigmine or edrophonium was administered at the commencement of recovery of the tetanic response. In the patient given two doses of neostigmine 2.5 mg, recovery of the tetanic and single twitch responses was complete in about 10 min, whereas in the patient given two doses of edrophonium 0.75 mg kg^{-1} the initial rapid antagonism of the blockade of the tetanic response was not sustained. However, antagonism of the single twich response was almost as effective as that by neostigmine.

A quantitative comparison of the antagonism of atracurium-induced neuromuscular blockade with neostigmine or edrophonium, given when recovery of the peak height of the tetanic contraction had reached approximately 50% of its initial height, is presented in table II. Differences in the percentage recovery between the neostigmine and edrophonium groups at reversal were not

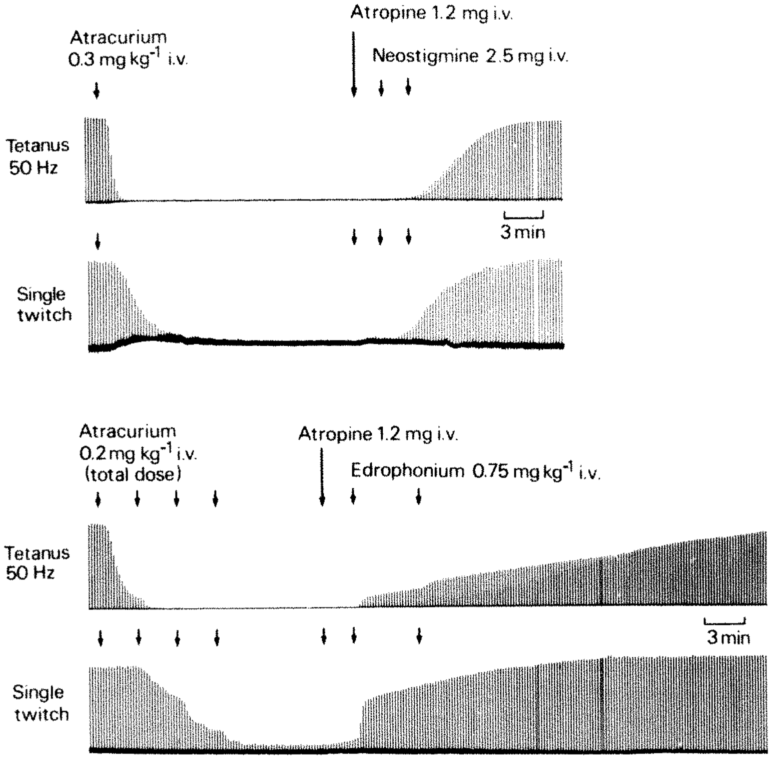

FIG. 1. Recordings of the tetanic and single twitch responses of the adductor pollicis muscles from two anaesthetized patients given atracurium 0.3 and 0.2 mg kg^{-1} i.v., respectively. In the patient given two doses of neostigmine 2.5 mg i.v., recovery of both responses was complete in about 10 min, whereas in the patient given two doses of edrophonium 0.75 mg kg^{-1} i.v. the initial rapid antagonism of the tetanic response was not maintained, but recovery of the single twitch response was almost as rapid as that after neostigmine.

TABLE II. *Antagonism of approximately 50% atracurium-induced blockade with neostigmine 2.5 mg i.v. (preceded by atropine 1.2 mg) and edrophonium 0.75 mg kg^{-1} i.v. (preceded by atropine 1.2 mg) using groups of five patients for each anticholinesterase. Mean values ± SEM. Significant differences:* *$^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$, respectively. ns = Not statistically significant*

	% Recovery of peak tetanic height at antagonism	Time(s) to max. recovery (min)		
		Tetanic response		Train-of-four response
Neostigmine	51.6 ± 3.2	202 ± 35	*	404 ± 26
	ns	*		***
Edrophonium	44.0 ± 6.3	89 ± 28	**	133 ± 28

significant. These results show that recovery of both the tetanic and train-of-four responses from blockade by atracurium was significantly faster after antagonism with edrophonium than with neostigmine. Observations were continued for up to 15 min after the administration of edrophonium and there was no evidence of residual curarization. Tracings of the tetanic and train-of-four contractions of the adductor pollicis muscles from two anaesthetized patients who were given atracurium 0.3 mg kg^{-1} i.v. are shown in figure 2. In one patient residual neuromuscular blockade was

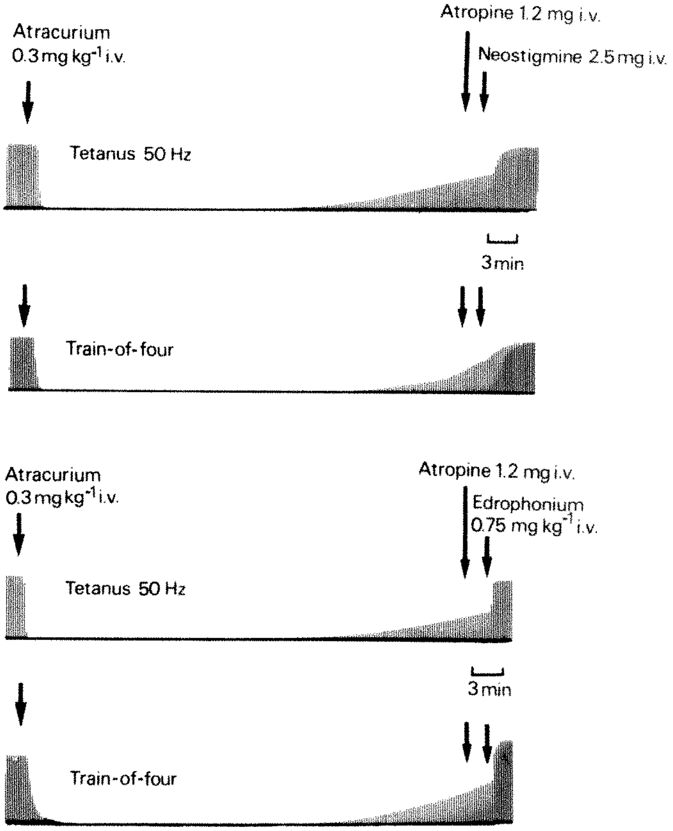

FIG. 2. Recordings of the tetanic and train-of-four responses of the adductor pollicis muscles from two anaesthetized patients given atracurium 0.3 mg kg^{-1} i.v. Antagonism from approximately 50% neuromuscular blockade was more rapid with edrophonium 0.75 mg kg^{-1} i.v. than with neostigmine 2.5 mg i.v.

antagonized with neostigmine 2.5 mg and in the other with edrophonium 0.75 mg kg^{-1}. It is evident from these recordings that recovery of the tetanic responses was more rapid after antagonism with edrophonium than with neostigmine. Recovery of the train-of-four responses followed a similar pattern.

DISCUSSION

In this study we have shown that the time taken to achieve 95% recovery of the tetanic response, when edrophonium was given at the commencement of recovery from atracurium-induced blockade, was not significantly different from that in a control group of patients who were not given an anticholinesterase. Furthermore, the rate of recovery after edrophonium was not appreciably increased after the administration of subsequent doses of the anticholinesterase. In contrast, recovery after neostigmine was significantly faster than in the control group. Bevan (1979) reported a similar pattern of recovery of the train-of-four response when edrophonium was administered as soon as muscle activity began to return after blockade by pancuronium. Recovery reached a plateau within 2 min and the subsequent recovery was slow. In another study, Harper, Bradshaw and Healy (1984) administered edrophonium when less than four responses of the train-of-four were present during recovery from alcuronium-induced neuromuscular blockade. They reported that in the first 1–2 min the train-of-four ratio was greater than in those patients given neostigmine, but during the following 5–35 min the initial rapid antagonism by edrophonium was not sustained and the ratio became less than that in the neostigmine group of patients.

If, however, recovery of the peak height of the tetanic contraction of the adductor pollicis muscle had reached approximately 50% of the pre-dose response then a large dose of edrophonium 0.75 mg kg^{-1} i.v. would effectively antagonize the neuromuscular blocking action. Furthermore, recovery of both the tetanic and train-of-four responses was significantly faster after edrophonium than after neostigmine and there was no evidence of recurarization. These findings are in agreement with other reports of rapid antagonism of the blockade produced by pancuronium, alcuronium and atracurium by large doses of edrophonium 0.5–1 mg kg^{-1} i.v. (Bevan, 1979; Kopman, 1979; Harper, Bradshaw and Healy, 1984; Jones, Pearce and Williams, 1984). In the present study we found it curious that recovery of the train-of-four response was significantly slower than that of the tetanic contraction after the administration of neostigmine and edrophonium. It would seem likely that relatively more acetylcholine should be available for receptor occupancy to antagonize neuromuscular block during train-of-four stimulation at 2 Hz because the decline in the output of the transmitter should be less than during repeated tetanic stimulation at 50 Hz, especially since we have no evidence to suggest that tetanic stimulation enhances recovery. Indeed, it has been a consistent finding of our studies that the tetanic response always recovers more slowly than the single twitch from competitive neuromuscular blockade. In the present study that pattern was followed.

In contrast to the tetanic response, the time taken for recovery of the single twitch response after antagonism with edrophonium was significantly shorter than that in the control group who were not given an anticholinesterase. However, it was significantly longer than after neostigmine. Other workers have reported that the first response of the train-of-four, regarded as a single twitch, recovered more rapidly than the fourth response and the train-of-four ratio (Bevan, 1979; Harper, Bradshaw and Healy, 1984; Jones, Pearce and Williams, 1984). Reliance on the return of the single twitch to the control value could be misleading, since a significant degree of residual receptor occupancy, as indicated by marked tetanic or train-of-four fade, may still be present (Ali et al., 1981; Payne and Hughes, 1981).

It is widely believed that tetanic or train-of-four fade is essentially a prejunctional effect, whereas the suppression of the single twitch occurs predominantly as the result of postjunctional receptor occupancy (Hubbard and Wilson, 1973; Bowman, 1980). Consequently, the single twitch recovers more rapidly than the tetanic and train-of-four responses during antagonism of atracurium-induced blockade with edrophonium because during high frequency stimulation the depletion in acetylcholine stores and reduced mobilization of the transmitter would favour longer receptor occupancy by the neuromuscular blocking drug.

The rapidity with which edrophonium acts may be related to its smaller molecular weight (166) compared with that of neostigmine (223) and a more rapid diffusion to its site of action than that achieved by neostigmine (Harper, Bradshaw and Healy, 1984). Another factor is that anticholinesterase drugs, in addition to their postsynaptic action in conserving the released acetylcholine, may also act presynaptically to increase the output of the transmitter from the motor nerve terminals. In this respect it has been claimed that edrophonium is particularly effective (Blaber, 1972). Thus, the rapid initial antagonism of competitive neuromuscular blockade by edrophonium may be associated with a rapid release of acetylcholine from the motor nerve terminal. The fact that the initial rapid antagonism by edrophonium is not maintained when the anticholinesterase is given at the commencement of recovery from neuromuscular blockade may be a result of transmission failure, because acetylcholine stores may be so rapidly depleted that mobilization cannot be maintained. It is also possible that the duration of action of edrophonium, even at relatively high doses, may be too short to sustain recovery from complete blockade. The anti-curare effect of edrophonium wanes if it is administered during complete neuromuscular blockade, because it is rapidly redistributed and excreted (Doughty and Wylie, 1952). However, if edrophonium is administered when spontaneous recovery from neuromuscular blockade is well established, it is unlikely that paralysis will recur because the plasma concentration of the blocking agent would be too low (Matteo, Spector and Horrowitz, 1974; Mcleod, Watson and Rawlins, 1976).

It has been suggested by Jones, Pearce and Williams (1984) that a train-of-four ratio of 50% provides a reasonable level of recovery for the safe antagonism of residual atracurium-induced blockade with appropriately large doses of edrophonium. In support of that view, we found that approximately 50% recovery of the peak tetanic contraction was an adequate value for effective antagonism by edrophonium. However, neostigmine should be used in preference to edrophonium when antagonism is required at the beginning of recovery, particularly that associated with the neuromuscular blockade induced by the longer acting competitive blocking agents, because the antagonism by neostigmine is more persistent and the recovery phase is significantly shortened. The determination of the extent of neuromuscular blockade and the effectiveness of the antagonist may require the use of a peripheral nerve stimulator.

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REAPPEARANCE OF THE TRAIN-OF-FOUR AFTER NEUROMUSCULAR BLOCKADE INDUCED WITH TUBOCURARINE, VECURONIUM OR ATRACURIUM

D. A. O'HARA, R. J. FRAGEN AND C. A. SHANKS

Muscular relaxation adequate to allow abdominal surgery is associated with a depression of the single evoked twitch response in excess of 75 percent of its control value (DeJong, 1966). An alternative quantitative assessment of residual neuromuscular blockade is provided by a train-of-four stimuli delivered in 2 s at 10-s intervals (Ali, Utting and Gray, 1971). The train-of-four ratio has its own internal control, and has been found to be a more sensitive index of the intensity of blockade than is the single twitch (Lee, 1975; Lee, Barnes and Katz, 1976; Ali and Savarese, 1976; Ali et al., 1981). At apparent full recovery of the single twitch, the T4:T1 ratio (ratio of the height of the fourth twitch to the first) can still be decreased. In 1975, using tubocurarine, Lee (1975) demonstrated that the disappearance and reappearance of each twitch of the train-of-four correlated with specified degrees of blockade. During recovery, the second twitch appears at 90% blockade of T1, the third at 80% blockade, and the fourth at 75% blockade. As a result, counting the number of responses to a train-of-four stimuli has become a clinically useful method for the intraoperative monitoring of neuromuscular blockade.

The purpose of this study was to examine the intensity of neuromuscular blockade present at the time of reappearance of the second, third and fourth twitches following blockade induced with atracurium or vecuronium, and to compare these with the values associated with tubocurarine-induced neuromuscular blockade.

SUMMARY

The characteristics of train-of-four recovery after atracurium or vecuronium were studied, under enflurane anaesthesia, and compared with those associated with tubocurarine-induced blockade. Ten patients each received vecuronium 0.1 mg kg^{-1}, atracurium 0.5 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1}. Neuromuscular blockade was calculated as the percent depression of the first twitch, and was determined at the time of reappearance of the second, third and fourth twitches of the train-of-four. The pattern during recovery from blockade induced by the three neuromuscular blocking agents was similar, with T2, T3 and T4 reappearing at approximately 93%, 89% and 86% residual blockade, respectively. These results are different from those previously reported by Lee (1975) indicating that, under enflurane anaesthesia, the train-of-four count may give an incorrect estimate of the degree of neuromuscular blockade.

PATIENTS AND METHODS

Seventeen males and 13 non-pregnant females (ASA physical status I or II) scheduled for elective operative procedures requiring neuromuscular blockade for intubation only, entered the study. The study was approved by the Institutional Review Board of Northwestern University, which granted permission to conduct the study without written informed consent. The procedures all lasted long enough to allow for spontaneous recovery of the fourth twitch. Patients were aged 20–60 yr and within 25% of ideal body weight (Bray, 1976).

The patients had no known renal, hepatic or

DORENE A. O'HARA*, M.D.; ROBERT J. FRAGEN, M.D.; COLIN A. SHANKS, M.D. F.F.A.R.C.S.; Department of Anesthesia, Northwestern University, Chicago, Illinois, U.S.A.

*Address for correspondence: Department of Anesthesia, U.M.D.N.J. Newark, 100 Bergen St, Newark, N.J. 07103, U.S.A.

neuromuscular disease, nor were they receiving drugs known to affect neuromuscular transmission in the preoperative period.

Patients were premedicated with a narcotic or a belladonna alkaloid, or both. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} i.v. and maintained with increments of fentanyl 50–100 µg and 1–2% enflurane (delivered concentration) in 50% nitrous oxide in oxygen, according to surgical requirements. Ventilation to normocarbia was maintained as measured by end-tidal carbon dioxide tension (Datex CO_2 monitor, Puritan–Bennett Corp.).

Each patient was randomly assigned to receive vecuronium 0.1 mg kg^{-1}, atracurium 0.5 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1}. The drugs were injected over 60 s to minimize the potential for hypotension with tubocurarine and atracurium.

Before the administration of the neuromuscular blocker, a Grass S48 stimulator provided supramaximal stimuli of 0.2 ms duration to the ulnar nerve at the elbow to obtain a steady control value. Train-of-four was recorded continuously from the thumb via a linear force transducer (Devices ST-10) and displayed on a Hewlett–Packard 7754B chart recorder.

The percent depression of the first twitch (control – T1/control) was then determined at the time of reappearance of the second, third and fourth twitches (T2, T3, T4), for each patient. The height of the first twitch was monitored during the remainder of the anaesthetic to ensure that the twitch height returned to control.

Mean values ± standard deviations for each agent, at each degree of train-of-four recovery, were calculated. Significance was determined by two-way analysis of variance (Snedecor and Cochran, 1967).

RESULTS

The mean ages, heights, and weights for each group are listed in table I. There were no statistically significant differences between these values in the three groups.

The mean durations of anaesthesia for the atracurium, vecuronium and tubocurarine groups were similar: 164 ± 126 min, 127 ± 78 min, and 197 ± 86 min, respectively.

The measured intensity of blockade at the times of reappearance of the second, third and fourth twitches for each agent are shown in table II. The mean percent blockade at the times of reappearance of T2, T3 and T4 were all found to be different from each other by the Newman–Keuls test ($P < 0.01$).

TABLE I. *Patient characteristics (means ± SD)*

	Atracurium	Vecuronium	Tubocurarine
Age (yr)	42 ± 10	40 ± 13	39 ± 5
Height (cm)	173 ± 10	169 ± 10	172 ± 9
Weight (kg)	76 ± 12	65 ± 14	70 ± 11

TABLE II. *Train-of-four results (mean ± SD)*

% Depression of T1 at reappearance of	Atracurium	Vecuronium	Tubocurarine
2nd Twitch	93 ± 3	93 ± 2	95 ± 2
3rd Twitch	89 ± 4	89 ± 4	90 ± 4
4th Twitch	86 ± 4	86 ± 6	87 ± 4

TABLE III. *Times (mean ± SD) to onset and recovery of blockade (min)*

	Atracurium	Vecuronium	Tubocurarine
Onset	1.3 ± 0.3	1.4 ± 0.4	1.2 ± 0.3
Maximum blockade	3.3 ± 1.0	3.8 ± 0.8	11.5 ± 8.0
T1 recovery	38 ± 10	27 ± 5	46 ± 18
T2 recovery	45 ± 11	34 ± 5	64 ± 31
T3 recovery	50 ± 10	37 ± 6	86 ± 32
T4 recovery	52 ± 10	39 ± 7	101 ± 29

The mean times to the onset of blockade (first depression of T1 (below control), to the maximum degree of blockade and to the reappearance of each twitch in the train-of-four are listed in table III.

There were no significant changes in end-tidal carbon dioxide concentration or temperature during the study. Delivered enflurane concentrations remained stable at 1–2% throughout the study.

DISCUSSION

The times to the onset of blockade and to recovery to 90% blockade (the time to reappearance of T3 in our study) are similar to previously reported values (Watts and Dillon, 1968; Hilgenberg, 1983; Bencini and Newton, 1984; Hunter, Jones and Utting, 1984; Miller et al., 1984).

The train-of-four data show a similar recovery pattern for atracurium, vecuronium and tubocurarine, with T2, T3 and T4 reappearing at approximately 93%, 89% and 86% residual neuromuscular blockade, respectively.

These results, however, are different from those of Lee (1975) (T2, T3, T4 reappearing at 90%, 80% and 75%). In that study, Lee used a number of agents which are now known to affect neuromuscular blockade. Some, but not all, of the patients received diazepam for premedication. Diazepam has been shown (Feldman and Crawley, 1970) to increase neuromuscular blockade. In addition, intubation was with the aid of suxamethonium in that study and, although 30 min elapsed before the administration of the non-depolarizing drug, it is probable that the prior dose of suxamethonium augmented the blockade (Katz, 1971). Blockade was antagonized in some of the patients in Lee's study, but times of the administration of the reversal agent were not detailed. Donati, Ferguson and Bevan (1983) have shown that, in antagonizing neuromuscular blockade, different reversal agents alter the characteristics of train-of-four and tetanic fade. It has been suggested that this occurs by differential binding of the anticholinesterase inhibitors to a presynaptic receptor (as yet unidentified).

Recent studies of neuromuscular blocking agents have indicated that train-of-four fade is the result of a presynaptic effect, and that neuromuscular blocking agents have different affinities for pre- and post-synaptic receptors (Blaber, 1973; Glavinovic, 1979; Williams, Webb and Calvey, 1980; Rang, 1981; Donati, Ferguson and Bevan, 1983; Jones et al., 1984; Robbins et al., 1984; Stanec and Baker, 1984). Bowman (1980), and Day and colleagues (1983), have indicated that vecuronium may have less of a presynaptic effect than previously available non-depolarizing drugs such as tubocurarine. As a result, vecuronium might be expected to cause less fade during onset and recovery than tubocurarine. Our results could not detect this effect.

It is possible that the use of different volatile anaesthetics could explain the difference between our results and those of Lee (1975). Lee (1975) used halothane; in this study we used enflurane. Rupp, Miller and Gencarelli (1984) have shown that enflurane has a more marked potentiating effect on vecuronium-induced neuromuscular blockade than halothane. Both *in vitro* (Kennedy and Galindo, 1975; Waud and Waud, 1975a, b) and *in vivo* (Lebowitz, Casey and Walts, 1970; Stanski et al., 1980) studies have shown that enflurane, even in low concentrations, potentiates the neuromuscular blocking effect of tubocurarine. This effect is thought to occur post-synaptically. If train-of-four fade is caused by a presynaptic effect, enflurane may affect twitch height more than fade. Whether halothane and enflurane affect *fade* to different degrees is not known.

Recently, Ham and Redpath (1985) reported, in abstract form, a similar train-of-four study with halothane anaesthesia using tubocurarine, atracurium, pancuronium, metocurine and gallamine, but not vecuronium. On recovery they found train-of-four characteristics similar to those of Lee's (1975) study with all of the neuromuscular blocking agents used. In their study, however, the train-of-four response was considered "absent" when it was diminished to 1–2% of control. This difference in criteria for complete blockade as well as the use of halothane might account for the difference between our results and those of Ham and Redpath.

In summary, the measured fade observed on train-of-four recovery was similar for the three drugs studied, and under enflurane anaesthesia occurred at greater degrees of blockade than reported previously. It is possible that, by counting the *observed* twitches in the train-of-four, the actual degree of blockade is incorrectly estimated.

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COMPARISON OF VISUAL AND MEASURED TRAIN-OF-FOUR RECOVERY AFTER VECURONIUM-INDUCED NEUROMUSCULAR BLOCKADE USING TWO ANAESTHETIC TECHNIQUES

D. A. O'HARA, R. J. FRAGEN AND C. A. SHANKS

SUMMARY

This study evaluated train-of-four recovery after the administration of vecuronium, comparing measured with visually observed responses. Responses to supramaximal stimuli of the ulnar nerves were measured by a force transducer, and compared with visually observed movements of the contralateral thumb. For the 10 patients anaesthetized with nitrous oxide and enflurane, the second, third and fourth twitches visually reappeared at 84 (±10) %, 76 (±11) %, and 70 (±12) % measured blockade, respectively. For the other 10 patients, anaesthetized with a narcotic–barbiturate technique, the second, third and fourth twitches reappeared at 81 (±8) %, 68 (±9) %, and 59 (±11) %. These results were not different for the two anaesthetic techniques.

Anaesthetists commonly rely on recovery of the train-of-four response to assess recovery from neuromuscular blockade. Using tubocurarine (in association with halothane anaesthesia), Lee (1975) visually observed the fifth finger of the hand when investigating the correlation between the observed and the measured responses. He found that the fourth, third and second twitches (T4, T3, and T2) of the train-of-four disappeared at 75, 80 and 90 % twitch depression, respectively, and reappeared in reverse order. One could, therefore, count the number of twitches seen on recovery from neuromuscular blockade and estimate the intensity of residual blockade.

In a recent study O'Hara, Fragen and Shanks (1986) measured train-of-four recovery (under enflurane anaesthesia) after the administration of vecuronium, atracurium or tubocurarine, the chart recorder showing that T2, T3 and T4 reappeared at approximately 93 %, 89 % and 86 % residual neuromuscular blockade, respectively, for all three drugs. Since the difference between these results and those of Lee (1975) may have been attributable to a difference in the effects of the volatile anaesthetic, we examined the effect of two anaesthetic techniques on the responses observed during vecuronium-induced neuromuscular blockade. In addition, we compared measured isometric contractions at the thumb with visually observed movements in the contralateral hand.

PATIENTS AND METHODS

The 13 males and seven non-pregnant females who entered the study (ASA physical status I or II) were scheduled for elective operative procedures requiring neuromuscular blockade. The study was approved by the Institutional Review Board of Northwestern University. The patients were aged from 20 to 60 yr, within 25 % of ideal body weight (Bray, 1976), without known renal, hepatic or neuromuscular disease, and had not received drugs known to affect neuromuscular transmission.

The 20 patients were either unpremedicated or received morphine sulphate 0.1 mg kg^{-1} and atropine 0.4 mg i.m. approximately 1 h before the

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DORENE A. O'HARA*, M.D.; ROBERT J. FRAGEN, M.D.; COLIN A. SHANKS, M.D., F.F.A.R.C.S., Department of Anesthesia, Northwestern University, Chicago, Illinois 60611, U.S.A.

* Address for correspondence: Department of Anesthesia, U.M.D.N.J. Newark, 100 Bergen St, Newark, N.J. 07103, U.S.A.

induction of anaesthesia in both groups, with thiopentone 3–5 mg kg^{-1} i.v.

Patients were randomly assigned, 10 to receive nitrous oxide–enflurane (group 1) and 10 to receive a nitrous oxide–narcotic–barbiturate anaesthetic (group 2). For patients in group 1, anaesthesia was maintained with 1–2% enflurane and 50% nitrous oxide in oxygen; in group 2, anaesthesia with 50% nitrous oxide and oxygen was supplemented with incremental doses of fentanyl 50–100 µg and thiopentone 50–100 mg according to surgical requirements. Since the measurements of recovery were to be made after at least 30 min of anaesthesia, it was felt the enflurane concentration would be at steady-state. End-tidal carbon dioxide tensions were measured continuously (Datex CO_2 monitor, Puritan-Bennett Corp.), and ventilation was adjusted to maintain normocarbia. Nasopharyngeal temperature was monitored continuously.

A Grass S48 stimulator provided train-of-four supramaximal stimuli of 0.2 ms duration to the ulnar nerve at the elbow every 10 s. A Hewlett-Packard 7754B chart recorder was used to monitor the train-of-four response recorded from the thumb via a linear force transducer. Trains-of-four supramaximal stimuli were applied to the contralateral ulnar nerve for visual assessment of the response at the thumb. After a stable train-of-four (four stimuli at 2 Hz at 10-s intervals) baseline was obtained, an intubating dose of vecuronium 0.1 mg kg^{-1} was administered. The train-of-four response was monitored until the first twitch regained control height.

The time to onset of blockade, time to maximum blockade and time to visually observed recovery of each twitch in the train-of-four were recorded. The percent twitch depression as measured by the force transducer was then determined at the time that each twitch in the train-of-four was discernible on the free hand by the one observer (D.O.) who could not see the recorded response.

Mean values ± standard deviations for the return of each twitch in the train-of-four, for each anaesthetic technique, were calculated. Two-way analysis of variance was used to compare the twitch responses for the two anaesthetic techniques, with repeat measures application within groups, followed by a Bonferroni t test. A P value of less than 0.05 was considered significant (Snedecor and Cochran, 1967).

TABLE I. *Times, after vecuronium 0.1 mg kg^{-1}, at which the four twitches were visually observed to have returned, and the concomitant intensities of (contralateral) twitch depression (mean (SD))*

Anaesthetic technique	Train-of-four reappearance			
	T1	T2	T3	T4
N_2O–narcotic				
Time (min)	31 (8)	36 (10)	40 (11)	43 (13)
Twitch depression (%)	92 (4)	81 (8)	68 (9)	59 (11)
Enflurane				
Time (min)	28 (7)	33 (9)	37 (9)	39 (10)
Twitch depression (%)	94 (3)	84 (10)	76 (11)	70 (12)

RESULTS

Neither temperature nor end-tidal carbon dioxide concentration changed significantly during the study. The mean ages, heights and weights (± SD) for the two groups were similar: group 1, 38 ± 9 yr, 167 ± 9 cm, and 65 ± 12 kg; group 2, 35 ± 9 yr, 170 ± 14 cm, and 71 ± 10 kg.

The mean times to the visually observed reappearance of each twitch are listed in table I. The mean times (± SD) to onset (first depression of T1 from control) and maximum blockade under enflurane anaesthesia were 1.3(±0.4) and 3.2(±0.8) min respectively. Under nitrous oxide–narcotic–barbiturate anaesthesia, these were 1.2(±0.3) and 3.0(±0.7) min, respectively. The measured intensity of blockade (control − T1)/control, at the times of visual recovery of each twitch in the train-of-four for each group are listed in table I. These values were not different for the two anaesthetic techniques.

DISCUSSION

Times to first onset of blockade and maximum blockade were similar to previously reported data (Nagashima et al., 1981; Buzello and Noldge, 1982; Bencini and Newton, 1984; Hunter, Jones and Utting, 1984), all measured under nitrous oxide–narcotic–barbiturate anaesthesia.

The measured intensities of blockade under enflurane anaesthesia were 94%, 84%, 76% and 70% for the visually observed reappearance of T1, T2, T3 and T4, respectively; under nitrous oxide–narcotic–barbiturate anaesthesia these were

92%, 81%, 68% and 59% for the visually observed reappearance of T1, T2, T3, and T4, respectively. These results are in general agreement with those of Lee (1975), despite differences in technique—such as his monitoring of the visual response at the fifth finger.

These results show greater recovery of blockade at each component of the train-of-four than that *measured* (with a force transducer) in our previous study (O'Hara, Fragen and Shanks, 1986), using enflurane along with vecuronium. This would indicate that the visually observed response has a sensitivity different from that of the measured response.

Ham and Redpath (1985) compared the manually felt with the measured train-of-four using halothane and five non-depolarizing neuromuscular blocking drugs: atracurium, pancuronium, tubocurarine, metocurine and gallamine. They found that, during the onset of blockade for tubocurarine, pancuronium and metocurine, the responses were similar to those reported by Lee (1975). For atracurium, the train-of-four disappeared at greater intensities of block; for gallamine at lesser. The train-of-four *reappeared* at similar intensities of blockade for all of the neuromuscular blocking agents used except gallamine (T2, T3 and T4 returning at 81%, 81% and 67%, respectively). While Ham and Redpath (1985) did not use diazepam, suxamethonium or antagonizing agents in their study, they did use a halothane anaesthetic and used tactile rather than visual observation of the train-of-four. Tactile and visual monitoring of the train-of-four have different sensitivities, tactile being more sensitive than visual (Viby-Mogensen, 1982).

Lee (1975) compared visually observed train-of-four responses of the fifth finger of the same hand in which the force transducer measured thumb contractions. As the fifth finger is less sensitive to neuromuscular blockade than the thumb (Shanks and Harrison, 1973) its train-of-four response might recover at a greater degree of blockade.

By the time that the third twitch in the train-of-four was observed in this study, with either anaesthetic technique, the threshold of adequate surgical relaxation had been reached. DeJong (1966) has indicated that 75% neuromuscular blockade at the hand correlates with adequate relaxation for abdominal surgery. The time between observation of T2 (adequate relaxation) and T3 (inadequate relaxation) in our study was 4 min with either anaesthetic (table I). Therefore, if the administration of additional doses of vecuronium is to be based on observation of the train-of-four, these doses should be given when T2, rather than T4, appears.

In summary, the observed recovery of the train-of-four with vecuronium occurred at a residual blockade of 90–95% for T1, 80–85% for T2, 70–75% for T3 and 60–70% for T4. There was no difference in this pattern of recovery between an enflurane compared with a nitrous oxide–narcotic anaesthetic technique. An average of 12 min elapsed between the return of the first and the fourth responses in the train-of-four, indicating the need for continuous, or at least frequent, monitoring during vecuronium-induced neuromuscular blockade.

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PHARMACOKINETICS OF GALANTHAMINE (A LONG-ACTING ANTICHOLINESTERASE DRUG) IN ANAESTHETIZED PATIENTS

P. WESTRA, M. J. S. VAN THIEL, G. A. VERMEER,
A. M. SOETERBROEK, A. H. J. SCAF AND H. A. CLAESSENS

SUMMARY

The pharmacokinetics of the long-acting anticholinesterase drug, galanthamine, were investigated in eight patients. After i.v. injection of 0.3 mg kg^{-1}, the decrease in the serum concentration of galanthamine followed a biexponential curve. The serum concentration decreased rapidly from 543 ± 47 ng ml^{-1} to 128 ± 14 ng ml^{-1} between 2 and 30 min with a $T_{\frac{1}{2}}^{\alpha}$ of 6.42 ± 2.15 min, and then declined more slowly with a $T_{\frac{1}{2}}^{\beta}$ of 264 ± 28 min. Total serum clearance of galanthamine amounted to 5.37 ± 0.87 ml min^{-1} kg^{-1}, and the renal clearance was 1.36 ± 0.10 ml min^{-1} kg^{-1}. The cumulative urinary excretion of galanthamine between 0 and 48 h after injection amounted to 28.0 ± 5.4% of the administered dose. The biliary excretion of galanthamine during 24 h amounted to 0.2 ± 0.1% of the dose. There was no evidence of glucuronide or sulphate conjugation of galanthampine.

Galanthamine is a tertiary amine of the phenanthrene group (fig. 1). It is an anticholinesterase and has been used to antagonize the neuromuscular blockade associated with the administration of curare-like agents (Stojanov, 1964; Cozanitis, 1971; DeAngelis and Walts, 1972; Baraka and Cozanitis, 1973). In addition, it has been used to reverse the respiratory depressant effect of opioids such as morphine, pethidine and dextromoramide, in animals and man (Paskov, Dobrev and Nikiforov, 1963; Cozanitis and Rosenberg, 1974; Cozanitis and Toivakka, 1974; Westra et al., 1982). Galanthamine may reverse the central anticholinergic syndrome caused by hyoscine (Baraka and Harik, 1977; Cozanitis, 1977) and certain central effects of droperidol and diazepam (Baraka, 1978). The recent finding that the anticholinesterase compounds, physostigmine and galanthamine, reversed opioid-induced respiratory depression in animals and man, but not the concomitant analgesia (Weinstock et al., 1980; Weinstock, Erez and Roll, 1981; Weinstock et al., 1982; Westra et al., 1982; Snir-Mor et al., 1983), makes galanthamine interesting pharmacologically. We have investigated the pharmacokinetics of galanthamine in anaesthetized patients.

PATIENTS AND METHODS

Patients

Eight female patients (group A), ASA Class I or II, aged 38–79 yr, weight 60–80 kg, undergoing minor gynaecological operations were studied after informed consent was obtained. Routine indices of liver and renal function were determined. Anaesthesia was induced with Althesin 4–5 ml and fentanyl 0.1 mg, and maintained with

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PIETER WESTRA*, M.D. PH.D. Institute of Anesthesiology, State University of Groningen, Groningen, The Netherlands.
MARTINUS J. S. VAN THIEL; ADRIANUS M. SOETERBROEK, PH.D.; Department of Clinical Pharmacy and Toxicology, Diaconessenhuis, Eindhoven, The Netherlands.
GUSTAAF A. VERMEER, M.D., PH.D., Department of Anesthesiology, Groot Ziekengasthuis, ’s-Hertogenbosch, The Netherlands and Departments of Pharmacology and Clinical Pharmacology, State University of Groningen, The Netherlands.
ARNOLDUS H. J. SCAF, PH.D., Departments of Pharmacology and Clinical Pharmacology, State University of Groningen, The Netherlands.
HENK A. CLAESSENS, University of Technology, Laboratory of Instrumental Analysis, Eindhoven, The Netherlands.
* Present address, for correspondence: Department of Anesthesiology, Ziekenhuis Leyenburg, P.O. Box 40551, 2504 LN ’s-Gravenhage, The Netherlands.

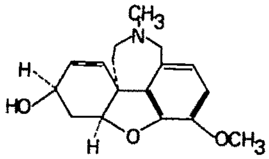

FIG. 1. Structural formula of galanthamine.

67% nitrous oxide in oxygen. Pancuronium 4–6 mg was given i.v. to produce neuromuscular blockade. At the end of surgery, galanthamine hydrobromide 0.3 mg kg^{-1} (0.234 mg as free base) was administered rapidly i.v. Venous blood samples (10 ml) were taken at 2, 5, 10, 20, 30, 60, 90, 120, 180, 240, 360, 480, 720, 960, 1200 and 1440 min thereafter. Urine was collected through a urinary catheter at regular intervals for 48 h.

In three female patients (group B), ASA Class I or II, aged 54–57 yr, weight 60–75 kg, undergoing cholecystectomy plus choledochotomy and insertion of a tightly fitting end-drain in the common bile duct, bile was collected at 12-h intervals for 24 h after the administration of the galanthamine. Routine indices of liver function were determined in group B.

Analysis of galanthamine

Concentrations of galanthamine in serum, urine and bile were measured by high-performance liquid chromatography (HPLC) (Claessens et al., 1983). The method of extraction was modified and included the use of Extrelut 3 cartridges (Merck, Darmstadt, GFR), based upon the liquid–liquid extraction principle. A serum sample was poured into the tube, which was pre-packed with an inert matrix of large surface area (diatomaceous earth).

The serum sample was prepared as follows: serum 0.5 ml + buffer 0.5 ml (ammonia solution 1 mol litre^{-1} titrated with hydrochloric acid 2 mol litre^{-1} to pH 9.0) + phenacetin 0.1 ml internal standard solution in methanol 900 μg ml^{-1}. Elution of galanthamine was carried out with three separate portions of dichloromethane 5 ml. The extraction solvent dichloromethane containing galanthamine passed freely through the column and, after subsequent evaporation under a gentle stream of nitrogen at 40 °C in a heating bath, HPLC determination of the final residue was performed.

Conjugation study

To investigate possible conjugation reactions of galanthamine (glucuronide or sulphate conjugation, or both), serum and urine samples in three patients (group A) and the bile samples from patients in group B were analysed.

Samples of 2 ml were adjusted to pH 5.0 by addition of hydrochloric acid 2 mol litre^{-1}. β-Glucuronidase solution 0.1 ml (No.G-0876), Sigma, St. Louis, U.S.A.) was added. The β-glucuronidase used contains both β-D-glucuronide glucuronohydrolase and arylsulphatase activity. The samples were incubated for 15 h in a water bath at 37 °C. Samples of 2 ml without addition of β-glucuronidase served as controls. After incubation all samples were analysed by HPLC.

Pharmacokinetic calculations

Serum galanthamine concentrations were fitted using a computerized iterative peeling program and the least squares method. Statistical analysis (Boxenbaum, Riegelman and Elashoff, 1974), gave the best fitting exponential function for the experimental data. The fit of the experimental data to the multi-exponential functions was compared statistically at the 95% significance level. The program determines the intercepts (C), slopes (λ) and half-lives ($T_{\frac{1}{2}}$) and, subsequently, calculates secondary parameters such as steady-state volume of distribution (V^{ss}), volume of the central compartment (V_1) and total serum clearance (Cl) according to the compartment model chosen (Wagner, 1976). The relative contribution of renal clearance (Cl_R) was calculated from total serum clearance (Cl) and the fraction of the dose of galanthamine excreted in urine ($Cl_R = Fe.Cl$). All values are given as mean ± SEM.

TABLE I. *Routine indices (mean ± SEM) of renal and liver function in serum in patients of group A, including ranges, and the ranges for normal adults*

	Total bilirubin (μmol litre^{-1})	GPT (u. litre^{-1})	GOT (u. litre^{-1})	Urea (mmol litre^{-1})	Creatinine (μmol litre^{-1})
Mean ± SEM	< 10	11 ± 1	14 ± 1	4.9 ± 0.7	66 ± 5
Range	—	7–14	10–16	3.4–6.7	51–82
Normal	0–17	0–30	0–40	3.3–6.7	62–106

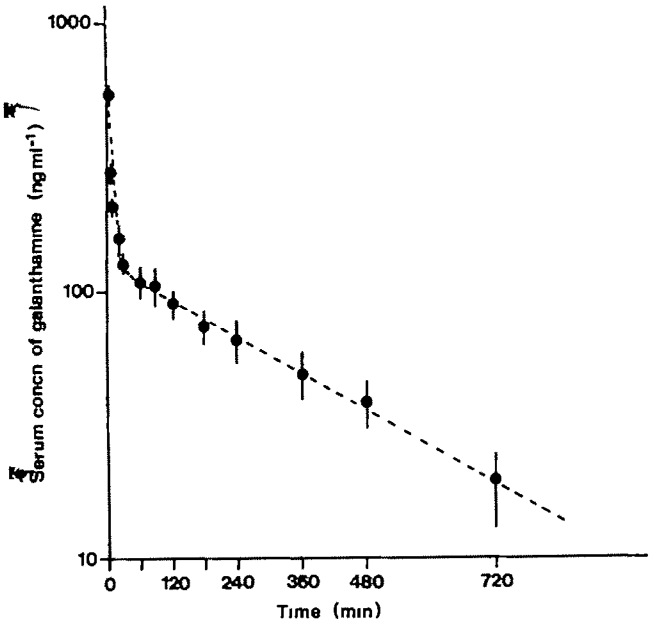

FIG. 2. Mean serum concentration–time profile of galanthamine in anaesthetized patients ($n = 8$) and the best fitting mean semilogarithmic plot. Vertical bars = SEM.

TABLE II. *Pharmacokinetic parameters (mean ± SEM) of galanthamine in anaesthetized patients* (n = *8*). *For explanation of symbols see text*

C_1	541 ± 101	ng ml^{-1}
C_2	125 ± 17	ng ml^{-1}
λ_1	0.176 ± 0.043	min^{-1}
λ_2	0.00278 ± 0.00025	min^{-1}
V_1	0.433 ± 0.094	litre kg^{-1}
V^{ss}	1.76 ± 0.23	litre kg^{-1}
$T_{\frac{1}{2}}^{\alpha}$	6.42 ± 2.15	min
$T_{\frac{1}{2}}^{\beta}$	264 ± 28	min
Cl	5.37 ± 0.87	ml min^{-1} kg^{-1}
Cl_R	1.36 ± 0.10	ml min^{-1} kg^{-1}

RESULTS

In group A, routine indices of renal and liver function were within their physiological limits (table I). The mean (range) urine volume was 2989 ± 474 (1555–3965) ml for the first 24 h and 2018 ± 452 (905–3320) ml for the second 24 h.

In group B, there were significant increases in the concentrations of the enzymes GOT and GPT, while the concentrations of alkaline phosphatase and total bilirubin were in the normal range. Bile production was 390 ± 138 (205–660) ml for the first 24 h.

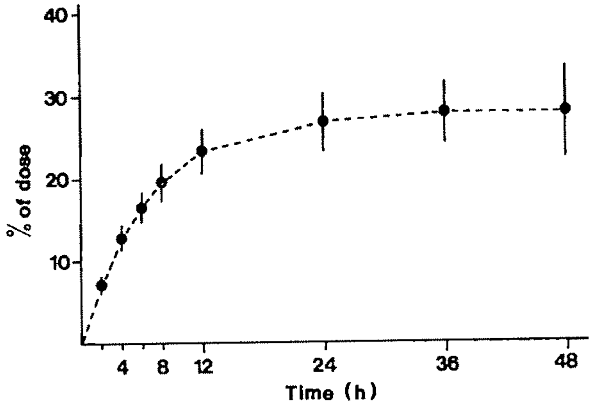

FIG. 3. Cumulative urinary excretion of galanthamine in anaesthetized patients ($n = 8$). Mean values ± SEM.

Pharmacokinetics of galanthamine

The decrease in the serum galanthamine concentration followed a biexponential function, as statistical analysis did not indicate significant improvement in the fit using more complex functions. The serum concentration of galanthamine decreased from a mean of 543 ± 47 ng ml^{-1} to 128 ± 14 ng ml^{-1} between 2 and 30 min with a $T_{\frac{1}{2}}^{\alpha}$ of 6.42 ± 2.15 min, and then declined more slowly with a $T_{\frac{1}{2}}^{\beta}$ of 264 ± 28 min (fig. 2).

No galanthamine could be detected in serum in any of the patients after 720 min, with 5 ng ml^{-1} as the minimal detectable concentration. The primary and secondary pharmacokinetic parameters of galanthamine are given in table II.

Recovery of galanthamine base from urine 48 h after injection varied widely in group A and ranged from 15.8 to 41.2% with a mean of 28.0 ± 5.4% of the administered dose (fig. 3). The cumulative urinary excretion showed only a minor increase after 24 h. Renal clearance (Cl_R) of galanthamine was 1.36 ± 0.10 ml min^{-1} kg^{-1}.

The biliary excretion of galanthamine during 24 h amounted to 0.2 ± 0.1% of the administered dose in group B.

Biotransformation

The chromatographic yields of the serum, urine and bile samples after enzymatic pretreatment with β-glucuronidase did not differ significantly from that of samples not treated with enzyme.

DISCUSSION

In this study the elimination half-life ($T_{\frac{1}{2}}^{\beta}$) of galanthamine was 264 min, whereas the anticholinesterase drugs neostigmine, pyridostigmine and edrophonium, used currently as antagonists of non-depolarizing neuromuscular blockade, have elimination half-lives of, respectively, 80, 46 and 114 min in man (Cronnelly et al., 1979; Morris et al., 1981; Williams, Calvey and Chan, 1983). Inhibition of serum cholinesterase for about 3 h has been reported after galanthamine (Paskov et al., 1962). For neostigmine and pyridostigmine this action was markedly shorter (Baraka et al., 1981). The durations of action of naloxone and physostigmine have been reported to be short compared with that of morphine (Evans et al., 1974; Weinstock et al., 1982). Long-acting anticholinesterase drugs could be of advantage in protecting patients from possible hazards such as the respiratory depression associated with opioids and during treatment with certain antibiotics in the postoperative period (Marshall, 1981).

The recovery of galanthamine from urine between 0 and 48 h averaged 28% of the administered dose. If renal excretion of galanthamine occurred solely by glomerular filtration, renal clearance of 1–2 ml min^{-1} kg^{-1} would be expected, which is in good agreement with a mean renal clearance of 1.36 ml min^{-1} in our patients (Duchin and Sechrici, 1978; Melman and Morelli, 1978). Hepatic uptake and biliary excretion, and biotransformation of galanthamine could contribute to non-renal clearance.

In comparison with the opioid phenanthrene derivatives (Johnson and Milne, 1981), possibilities of biotransformation of galanthamine are O-demethylation and conjugation at C3, N-demethylation and conjugation at C7. Our investigations exclude the possibility of glucuronide and sulphate conjugation. The biliary excretion of galanthamine is negligible.

We conclude that, from the pharmacokinetic point-of-view, galanthamine is suitable to reverse the unwanted effects and side-effects of long-acting drugs, but further pharmacological studies of galanthamine and possible analogues are necessary.

ACKNOWLEDGEMENTS

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A SHEEP PREPARATION FOR STUDYING INTERACTIONS BETWEEN BLOOD FLOW AND DRUG DISPOSITION

VI: EFFECTS OF GENERAL OR SUBARACHNOID ANAESTHESIA ON BLOOD FLOW AND CHLORMETHIAZOLE DISPOSITION

W. B. RUNCIMAN, L. E. MATHER, A. H. ILSLEY, R. J. CARAPETIS AND R. N. UPTON

SUMMARY

Blood flow through and chlormethiazole extraction ratios across lungs, liver, kidneys and gut were measured in awake unrestrained sheep (controls) and with the same animals anaesthetized with 1.5% halothane or whilst undergoing high thoracic subarachnoid blockade with amethocaine. In the control-drug studies, chlormethiazole infused to sub-sedative blood concentrations produced no significant changes in haemodynamics or in the kinetics of iodohippurate (renal and hepatic blood flows). Chlormethiazole was eliminated predominantly by the liver (mean extraction ratio and clearance, respectively, 0.90 and 1.3 litre min^{-1}) and lungs (0.15; 0.6 litre min^{-1}). Renal clearance was absent or negligible (>0.1 litre min^{-1}). Because of pulmonary clearance, mean total body clearance was derived from analysis of pulmonary arterial concentrations. Under general anaesthesia, there were significant reductions in mean cardiac output, hepatic and renal blood flow (to 54%, 63% and 43% of control); chlormethiazole mean hepatic extraction ratios and clearance were reduced, respectively, to 82% and 56% of control, and its pulmonary and renal clearances were abolished. With subarachnoid anaesthesia there were no significant changes in haemodynamics or in chlormethiazole extraction ratios or clearances.

Since general anaesthesia and subarachnoid anaesthesia may influence the cardiovascular system (Prys-Roberts, 1980; Greene, 1981), we have studied their effects on the disposition of selected drugs with potentially flow-limited clearances using sheep with chronically implanted catheters (Runciman, Ilsley et al., 1984; Runciman, Mather et al., 1984a). In this paper, studies on the disposition of chlormethiazole are presented. Chlormethiazole is used in the management of acute alcohol withdrawal (Glatt, George and Frisch, 1965) and as an anti-convulsant in pre-eclamptic toxaemia (Duffus et al., 1969). It has been used as an i.v. sedative for minor procedures (Galizia, Metreweli and Prout, 1975), as an adjunct to regional anaesthesia (Seow, Mather and Cousins, 1985), and to facilitate the management of patients requiring intensive care (Scott et al., 1980). In man, the infusion of chlormethiazole to produce mild sedation may cause a moderate tachycardia but, generally, no significant change in cardiac output (Wilson, Stephen and Scott, 1969; Scott et al., 1980; Seow Mather and Roberts, 1981). Chlormethiazole was chosen in order to study the effects of general or subarachnoid anaesthesia on the disposition of a drug potentially having perfusion-limited hepatic clearance and suspected of having pulmonary and renal metabolic clearance (Mather et al., 1981).

MATERIALS AND METHODS

Design of study

Studies were carried out in sheep according to the standard design developed to study, concur-

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WILLIAM B. RUNCIMAN, F.F.A.R.A.C.S., PH.D.; LAURENCE E. MATHER, PH.D., F.F.A.R.A.C.S.; ANTHONY H. ILSLEY, PH.D.; RONDA J. CARAPETIS, DIP. LAB. MED.; RICHARD N. UPTON, B.SC.; Department of Anaesthesia and Intensive Care, Flinders Medical Centre, The Flinders University of South Australia, Adelaide, S.A. 5042, Australia.

Correspondence to L.E.M.

rently, interactions between blood flow and drug disposition. The rationale for the choice of species, the preparation of the animals for study, and the demonstration of maintenance of normal physiological function over the study period, have been presented in detail previously (Runciman, Ilsley et al., 1984; Runciman, Mather et al., 1984a). A brief description of those aspects pertaining to the disposition of chlormethiazole is given here.

Sheep were acclimatized to metabolic crates and then, under general anaesthesia, multiple (including a left renal vein, a right hepatic vein and pulmonary artery) intravascular catheters were placed via the right jugular vein, and into the ascending aorta via the right carotid artery. Additional catheters were placed in the mesenteric and portal veins via an abdominal incision. The catheters were attached to a flushing system, and 2 weeks was allowed for the sheep to recover from the procedure. Cardiac output was measured by dye and thermodilution, renal blood flow by the Fick method using sodium ^{125}I-iodohippurate (IOH) and liver blood flow using the indicator dilution principle with IOH infused to the mesenteric vein catheter (Runciman, Ilsley et al., 1984). By simultaneous sampling from the catheters, blood flow through, and chlormethiazole extraction ratios across, the kidney, lungs, liver and gastrointestinal tract could be measured repeatedly.

Three studies in sheep under 1.5% halothane general anaesthesia (studies designated GA1–GA3) were each compared with control-drug studies in the same animals awake (C1–C3), and three studies in sheep under high thoracic subarachnoid anaesthesia (to approximately T4) (SAi–SAiii) were each compared with control-drug studies in the same animals (Ci–Ciii). Study pairs were separated by at least 2 days (Runciman, Mather et al., 1984b). In each control-drug study, control measurements of cardiac output, renal blood flow, hepatic blood flow, arterial pressure and heart rate were obtained every 10 min for 1 h (seven sets). Chlormethiazole ethanedisulphonate 0.8% was then infused to the right atrium using a two-stage infusion designed to achieve steady-state conditions rapidly; a loading infusion of between 14.1 and 14.5 mg min^{-1} for 15 min was followed immediately by a maintenance infusion of between 7.0 and 7.3 mg min^{-1} for 75 min. Arterial blood samples were taken every 5 min for 30 min after the start of the 15-min loading infusion and for 30 min after cessation of the 75-min maintenance infusion. Haemodynamic measurements and blood samples from all appropriate sites were obtained every 10 min during the chlormethiazole maintenance infusion. The last 60-min period of the chlormethiazole maintenance infusion was regarded as the basis for determining chlormethiazole disposition data, and for the comparison of haemodynamic data with those obtained in the control period before the chlormethiazole infusion.

In each general anaesthesia study, the control period was shortened to four sets of measurements made 10 min apart, anaesthesia was induced with sodium thiopentone 20 mg kg^{-1} i.v., a cuffed tracheal tube was inserted, and anaesthesia was maintained with halothane in 40% oxygen (balance nitrogen). A constant volume ventilator provided intermittent positive pressure ventilation. The vaporizer and ventilator were adjusted to maintain the expired halothane concentration at 1.5% and the expired carbon dioxide concentration at 5%. After induction of anaesthesia, the sheep was placed in its "normal" lying position with the legs tucked comfortably beneath it. The sternum and forelegs were supported on a foam rubber bolster so that the abdomen was not subject to compression. After 60 min, chlormethiazole was infused and measurements made using a regimen identical to the control-drug study. Saline 0.9%, up to a total of 200 ml, was infused i.v. as required; mean arterial pressure was maintained within 15% of control values.

In each subarachnoid anaesthesia study, four sets of control measurements were obtained (as in the general anaesthesia studies). After skin preparation, a 20-gauge spinal needle was inserted to the subarachnoid space in the lumbar region and 10% amethocaine hydrochloride 5 ml was injected over 5 s with barbotage. Saline 0.9%, up to a total of 200 ml, was infused i.v. at this stage; mean arterial pressure was maintained within 14% of control values. The blockade was allowed to stabilize and the posture of the sheep was adjusted as in the general anaesthesia studies. The segmental level of blockade was monitored by observing reflex flicking of the skin in response to prodding with a finger (Lebeaux, 1975). After 60 min, chlormethiazole was infused and measurements were made according to the regimen used in the control-drug and general anaesthesia studies. The blockade did not start to regress until 160 min had elapsed, but had always started to regress by 180 min.

The haemodynamic variables during the last 60 min of the chlormethiazole maintenance infusion in each general anaesthesia and subarachnoid anaesthesia study were each expressed as a percentage of the mean value of the corresponding variable on that day in the same animal during the control period preceding the infusion of the drug, and were compared using Student's *t* test. As the effects of general and subarachnoid anaesthesia on regional blood flow and oxygen tensions have been discussed in detail in a separate communication (Runciman, Mather et al., 1984b), only those haemodynamic changes which directly affect the measurement or interpretation of chlormethiazole disposition are reported in detail in this paper.

Chlormethiazole analysis and disposition

Chlormethiazole concentrations in whole blood were determined by gas–liquid chromatography with nitrogen selective detection after solvent extraction (Seow et al., 1981) and were expressed as the ethanedisulphonate salt.

Chlormethiazole clearances by lungs, kidney, liver and gastrointestinal tract were calculated from the products of relevant organ blood flows and extraction ratios during the last 60 min of the chlormethiazole maintenance infusion. Because pulmonary clearance of chlormethiazole was confirmed, the mean total body clearance was calculated as the ratio of the rate of the maintenance infusion to the mean pulmonary arterial chlormethiazole concentration. These calculations are derived from application of the Fick principle. Thus, strictly, they apply to steady-state conditions which, in fact, were not achieved in every study. Non-steady-state would tend to underestimate the mean total body clearance and overestimate the regional clearances. However, the consequence of such errors was judged to be insignificant from comparison with results derived from integrated drug concentration curves. To assist in the interpretation of the effects of anaesthesia, the mean hepatic intrinsic clearance, that is, the hypothetical clearance in the absence of any limitation imposed by hepatic perfusion, was determined from the ratio of the mean hepatic clearance of chlormethiazole to the transmitted fraction (1 − hepatic extraction ratio) (Wilkinson and Shand, 1975; Branch, 1982). This assumes that the hepatic clearance of chlormethiazole is adequately represented by the "well stirred" model—a finding that has been justified for other drugs (such as pethidine and lignocaine) which have similarly high clearances by the rat liver *in vitro* (Ahmad, Bennett and Rowland, 1983). The disposition characteristics of chlormethiazole during each individual general and subarachnoid anaesthesia study were each expressed as percentages of the mean value of the corresponding index during the control-drug study in the same animal and were compared using Student's *t* test for paired data.

RESULTS

Control-drug studies

The chlormethiazole infusion regimen used in these studies produced mild sedation only. During this period, the mean values for the haemodynamic and IOH kinetic indices remained within 4% of their corresponding control values before the chlormethiazole infusion, with the exception of the hepatic blood flow and hepatic fraction of cardiac output (table I). Although these varied between animals, the overall mean values were, respectively, 128 and 125% of their control values; however, these changes were not significant.

There was substantial hepatosplanchnic and pulmonary extraction of chlormethiazole (fig. 1, tables II and III). During the steady-state period, the mean hepatosplanchnic extraction ratios ranged from 0.85 to 0.92. This was principally hepatic, but there was a small net, but extremely variable, extraction of chlormethiazole across the gastrointestinal tract. Pulmonary extraction always occurred with mean extraction ratios of 0.09 to 0.25 in different studies. Mean renal extraction ratios ranged from almost zero to 0.09.

The mean total body clearance of chlormethiazole calculated from arterial concentrations was consistently high and varied from 1.87 to 3.47 litre min^{-1} (mean 2.78, SD 0.62 litre min^{-1}). The summed measured hepatic, pulmonary and renal clearances in the steady-state period accounted for 70 (SD 14) % of the mean total body clearance and varied from 53% to 94% in individual studies (tables II and III).

General anaesthesia studies

Typical effects of general anaesthesia on chlormethiazole blood concentrations and clearances are shown in figure 1, and a summary of the relevant results is shown in figure 2. Under general anaesthesia, chlormethiazole blood concentrations were approximately doubled and there

TABLE I. *Effect of chlormethiazole on blood flow and iodohippurate kinetics in the control-drug studies. Values for cardiac output (CO), hepatic blood flow (HBF), renal blood flow (RBF), iodohippurate renal extraction ratio (IOH ER) and clearance (IOH Cl) before the chlormethiazole infusion in the control-drug studies (C) may be compared with values obtained during the last 60 min of the chlormethiazole maintenance infusion. *Mean value only: obtained from difference of mean hepatic venous and arterial IOH concentrations. (Catheter wedged, causing fluctuations in IOH hepatic venous concentrations)*

	Before chlormethiazole infusion (7 sets of determinations, 10 min apart over 60 min)					During chlormethiazole infusion (6 sets of determinations, 10 min apart over 60 min)				
Study	CO (litre min^{-1})	HBF (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})	CO (litre min^{-1})	HBF (litre min^{-1})	RBF (litre min^{-1})	IOH ER	IOH *Cl* (litre min^{-1})
C1										
Mean	3.3	1.21	0.56	0.73	0.41	3.0	1.28	0.51	0.70	0.36
SD	(0.3)	(0.42)	(0.03)	(0.01)	(0.02)	(0.4)	(0.23)	(0.02)	(0.01)	(0.01)
C2										
Mean	2.2	0.75	0.61	0.61	0.37	2.7	1.45	0.62	0.60	0.37
SD	(0.2)	(0.28)	(0.06)	(0.06)	(0.02)	(0.2)	(0.34)	(0.04)	(0.02)	(0.01)
C3										
Mean	2.9	1.4	0.67	0.65	0.42	3.1	1.4*	0.70	0.61	0.42
SD	(0.3)		(0.04)	(0.05)	(0.01)	(0.2)		(0.04)	(0.02)	(0.01)
Ci										
Mean	4.1	1.34	0.68	0.74	0.50	4.4	1.57	0.73	0.69	0.50
SD	(0.6)	(0.32)	(0.08)	(0.02)	(0.03)	(0.8)	(0.25)	(0.06)	(0.02)	(0.03)
Cii										
Mean	3.8	1.24	0.65	0.63	0.40	3.5	1.16	0.61	0.61	0.37
SD	(0.4)	(0.20)	(0.03)	(0.01)	(0.02)	(0.31)	(0.09)	(0.03)	(0.02)	(0.01)
Ciii										
Mean	3.3	1.21	0.65	0.73	0.41	3.0	1.28	0.51	0.70	0.36
SD	(0.3)	(0.42)	(0.03)	(0.01)	(0.02)	(0.4)	(0.23)	(0.02)	(0.01)	(0.01)

were significant reductions in cardiac output, hepatic and renal blood flow ($P < 0.05$, one-tail test) (tables II and IV). All haemodynamic variables were within 10% of those reported previously for general anaesthesia (Runciman, Mather et al., 1984b).

The chlormethiazole hepatic extraction ratio, clearance, and intrinsic clearance under general anaesthesia decreased to mean values of 82, 56, and 22% of the corresponding values observed in the control-drug studies. The pulmonary extraction of chlormethiazole was abolished. Thus, it may be concluded that the pulmonary intrinsic clearance was also abolished (table II). Similarly, any renal extraction was abolished also. These reductions were significant ($P < 0.05$, one-tail test) except for the reduction in chlormethiazole hepatic extraction ratio; the P value in this instance was 0.066. Under general anaesthesia, the mean total body clearances ranged from 0.91 to 1.59 litre min^{-1}, representing an average of 50% of the values obtained in control-drug studies, while the summed hepatic, pulmonary and renal clearances accounted for 48–65% of the mean total body clearances.

Subarachnoid anaesthesia studies

Under subarachnoid anaesthesia, all the mean haemodynamic variables during the steady-state period remained within 10% of their corresponding values during the control period on that day (table V).

Typical effects of subarachnoid anaesthesia on chlormethiazole blood concentrations and clearances are shown in figure 1 and table III, and a summary of the relevant results is presented in figure 2. Chlormethiazole hepatic extraction ratio, clearance, and intrinsic clearance were means of 96, 110 and 89% of their corresponding values in control-drug studies. Chlormethiazole pulmonary extraction ratio, clearance and intrinsic clearance were means of 96, 109, and 107% of their values in the corresponding control-drug studies. None of these changes was statistically significant. The total clearance of chlormethiazole accounted for by the sum of the directly measured regional clearances averaged 77% of the mean total body clearance (table III).

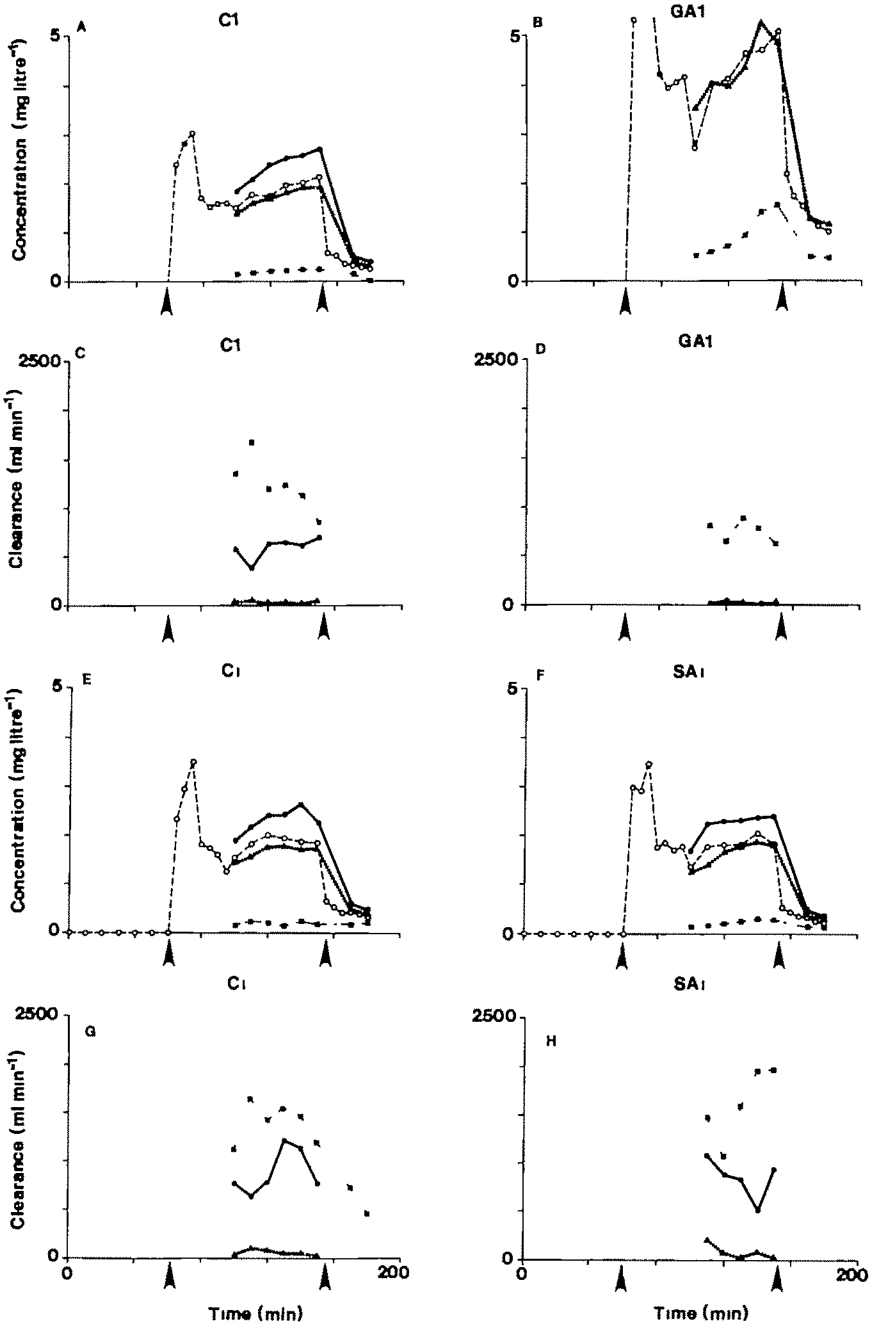

FIG. 1. Typical paired chlormethiazole control-drug and anaesthesia studies. The arrows denote the beginning and ending of the chlormethiazole infusion. Note the large arterial–hepatic vein chlormethiazole concentration difference and the smaller pulmonary–arterial and arterial–renal vein chlormethiazole concentration differences. Blood concentrations of chlormethiazole in control-drug studies (panels A and E) may be compared with corresponding general (GA) (panel B) and subarachnoid (SA) (panel F) anaesthesia studies. Chlormethiazole clearances in control drug-studies (panels C and G) may be compared with corresponding general (panel D) and subarachnoid (panel H) anaesthesia studies. ○—○ = Arterial; ●——● = pulmonary; ■---■ = hepatic; ▲...▲ = renal.

TABLE II. *Effects of general anaesthesia on chlormethiazole disposition. Values for chlormethiazole pulmonary arterial blood concentrations* (*Cb*), *mean total body clearance* (Cl), *hepatic extraction ratio* (*ERh*) *and clearance* (Cl*h*) *pulmonary extraction ratio* (*ER*$_p$) *and clearance* (Cl$_p$) *and renal extraction ratio* (*ERr*) *and clearance* (Clr) *for the last 60 min of the chlormethiazole infusion in the control-drug* (*C*) *studies may be compared with those in the same animal during the corresponding period in general anaesthesia* (*GA*) *studies*

	Control-drug studies (7 sets of determinations, 10 min apart over 60 min)								General anaesthesia studies (6 sets of determinations, 10 min apart over 60 min)							
Study	*C*b (mg litre^{-1})	*Cl* (litre min^{-1})	ERh	*Cl*h (litre min^{-1})	ERp	*Cl*p (litre min^{-1})	ERr	*Cl*r (litre min^{-1})	Study	*C*b (mg litre^{-1})	*Cl* (litre min^{-1})	ERh	*Cl*h (litre min^{-1})	ERp	*Cl*p (litre min^{-1}	ERr	*Cl*r (litre min^{-1})
C1									GA1								
Mean	2.4	2.99	0.89	1.25	0.20	0.60	0.08	0.04	Mean	4.5	1.59	0.79	0.76	~0	~0	~0	~0
SD	(0.3)		(0.01)	(0.28)	(0.04)	(0.11)	(0.03)	(0.02)	SD	(0.5)		(0.07)	(0.10)				
C2									GA2								
Mean	3.8	1.87	0.92	1.33	0.16	0.43	~0	~0	Mean	6.8	1.07	0.83	0.54	~0	~0	~0	~0
SD	(0.5)		(0.04)	(0.33)	(0.09)	(0.15)			SD	(0.7)		(0.08)	(0.22)				
C3									GA3								
Mean	3.3	2.18	0.91	1.3	0.09	0.28	~0	~0	Mean	7.9	0.91	0.62	0.59	~ 0	~0	~0	~0
SD	(0.5)		(0.02)	(0)	(0.03)	(0.16)			SD	(0.5)		(0.14)	(0.15)				

TABLE III. *Effects of subarachnoid anaesthesia on chlormethiazole disposition. Values for chlormethiazole steady state pulmonary arterial blood concentration* (*Cb*), *mean total body clearance* (Cl), *hepatic extraction ratio* (*ERh*) *and clearance* (Cl*h*), *pulmonary extraction ratio* (*ERp*) *and clearance* (Cl*p*) *and renal extraction ratio* (*ERr*) *and clearance* (Clr) *for the last 60 min of the chlormethiazole maintenance infusion in the control-drug* (*C*) *studies may be compared with those in the same animal during the corresponding period in subarachnoid anaesthesia* (*SA*) *studies.* * *Mean of two samples taken before a period of non-steady-state probably caused by gastric emptying*

	Control-drug studies (7 sets of determinations, 10 min apart over 60 min)								Subarachnoid anaesthesia studies (6 sets of determinations, 10 min apart over 60 min)							
Study	*C*b (mg litre^{-1})	*Cl* (litre min^{-1})	ERh	*Cl*h (litre min^{-1})	ERp	*Cl*p (litre min^{-1})	ERr	*Cl*r (litre min^{-1})	Study	*C*b (mg litre^{-1})	*Cl* (litre min^{-1})	ERh	*Cl*h (litre min^{-1})	ERp	*Cl*p (litre min^{-1})	ERr	*Cl*r (litre min^{-1})
Ci									SAi								
Mean	2.3	3.16	0.90	1.40	0.21	0.89	0.09	0.07	Mean	2.2	3.16	0.88	1.63	0.19	0.86	0.09	0.09
SD	(0.3)		(0.02)	(0.20)	(0.05)	(0.23)	(0.03)	(0.03)	SD	(0.3)		(0.03)	(0.37)	(0.03)	(0.19)	(0.08)	(0.07)
Cii									SAii								
Mean	2.1	3.47	0.85	0.96	0.25	0.86	~0	~0	Mean	2.4	2.92	0.80	1.30*	0.33	1.40	~0	~0
SD	(0.2)		(0.04)	(0.09)	(0.06)	(0.21)			SD	(1.0)							
Ciii									SAiii								
Mean	2.4	2.99	0.89	1.25	0.20	0.60	0.08	0.04	Mean	2.6	2.80	0.87	1.06	0.13	0.47	0.13	0.07
SD	(0.3)		(0.01)	(0.28)	(0.07)	(0.11)	(0.03)	(0.02)	SD	(0.3)		(0.04)	(0.15)	(0.10)	(0.38)	(0.11)	(0.06)

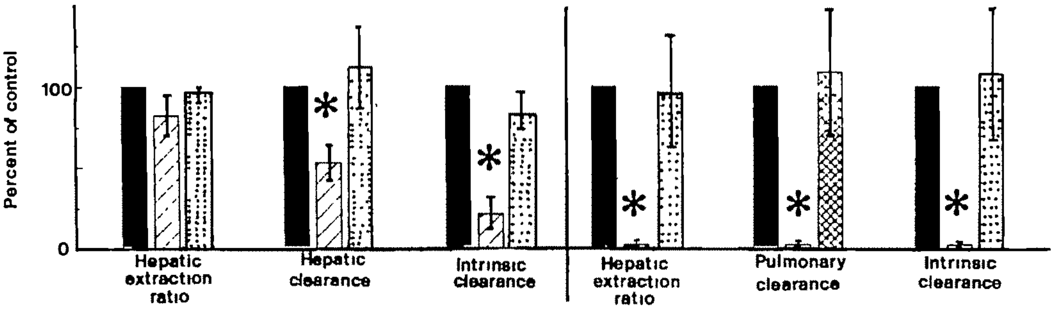

FIG. 2. Effects of anaesthesia on chlormethiazole hepatic kinetics. The mean values and standard deviations of the chlormethiazole hepatic and pulmonary extraction ratios, clearances and intrinsic clearances during the steady-state period of GA (cross-hatched columns) and SA (stippled columns) studies were each expressed as percentages of the mean value of the corresponding parameter in the control-drug study (black columns) in the same animal. *$P < 0.05$.

TABLE IV. *Effect of general anaesthesia and chlormethiazole on blood flow. Values for cardiac output (CO), hepatic blood flow (HBF), renal blood flow (RBF), in the control period before the general anaestheisa may be compared with values obtained during the last 60 min of the chlormethiazole maintenance infusion during general anaesthesia*

	Before GA and chlormethiazole infusion (4 sets of determinations, 10 min apart over 60 min			During GA and chlormethiazole infusion (6 sets of determinations, 10 min apart over 60 min)		
Study	CO (litre min^{-1})	HBF (litre min^{-1})	RBF (litre min^{-1})	CO (litre min^{-1})	HBF (litre min^{-1})	RBF (litre min^{-1})
GA1						
Mean	3.7	1.60	0.63	1.9	0.97	0.36
SD	(0.8)	(0.30)	(0.09)	(0.1)	(0.13)	(0.03)
GA2						
Mean	3.3	0.89	0.53	2.0	0.54	0.17
SD	(0.1)	(0.13)	(0.11)	(0.2)	(0.10)	
GA3						
Mean	3.6	1.45	0.95	1.8	0.96	0.31
SD	(0.3)	(0.35)	(0.14)	(0.3)	(0.33)	(0.05)

DISCUSSION

There were no significant changes in haemodynamics or IOH kinetics during the infusion of chlormethiazole in awake animals during the control-drug studies or under subarachnoid anaesthesia with fluid preload. In marked contrast, there were reductions in these values under general anaesthesia (Runciman, Mather et al., 1984b).

Under halothane anaesthesia, the mean total body clearance, hepatic, pulmonary and renal extraction ratios and clearances of chlormethiazole were decreased significantly. The effects of halothane anaesthesia in decreasing the regional clearances of chlormethiazole add one more drug to the list of potential pharmacokinetic drug interactions associated with halothane anaesthesia (Runciman and Mather, 1986). Under subarachnoid anaesthesia, there were no significant changes in any of these pharmacokinetic indices.

It is apparent that regional clearances of chlormethiazole were not constant throughout the studies. There were no obvious systematic reasons for this. The clearances determined reflected minute-to-minute variability in measured blood flow and drug extraction ratio—both being subject to physiological, analytical and statistical vagaries. While the first of these may be

TABLE V. *Effects of subarachnoid anaesthesia and chlormethiazole on blood flow. Values for cardiac output (CO), hepatic blood flow (HBF), renal blood flow (RBF) in the control period before spinal anaesthesia may be compared with values obtained during the last 60 min of the chlormethiazole maintenance infusion during subarachnoid anaesthesia*

	Before SA and chlormethiazole infusion (4 sets of determinations, 10 min apart over 60 min)			During SA and chlormethiazole infusion (6 sets of determinations, 10 min apart over 60 min)		
Study	CO (litre min^{-1})	HBF (litre min^{-1})	RBF (litre min^{-1})	CO (litre min^{-1})	HBF (litre min^{-1})	RBF (litre min^{-1})
SAi						
Mean	4.4	1.83	0.97	4.5	1.86	1.01
SD	(0.5)	(0.26)	(0.04)	(0.5)	(0.48)	(0.06)
SAii						
Mean	3.6	1.57	0.60	4.1	1.61	0.53
SD	(0.3)	(0.01)	(0.08)	(0.4)	(0.19)	(0.05)
SAiii						
Mean	3.6	1.43	0.60	3.6	1.23	0.58
SD	(0.5)	(0.33)	(0.01)	(0.3)	(0.23)	(0.04)

minimized by the use of *in vitro* preparations, this will be at the expense of not insignificant assumptions of preparation viability and dubious extrapolation to the *in vivo* situation.

The clearance of drugs by the lungs has special significance to anaesthetists. Previous opportunistic studies in man suggested that there may be pulmonary clearance of chlormethiazole (Mather et al., 1981) and this has been confirmed in these more systematic studies. It was pointed out recently that "the lungs efficiently remove many amino compounds from the circulation" (Roth, 1984)—a view supported by a variety of studies performed in lung tissue *in vitro* or lung perfusion preparations *in situ*. However, it is not always clear from the literature whether this "removal" refers to drug distribution into or clearance by lung tissue, as most of the investigations cited were not performed at or near steady-state. Ignoring pulmonary clearance creates a systematic error in all pharmacokinetic characteristics calculated from mass of drug (e.g. total body clearance, apparent volume of distribution). Thus, for substances having pulmonary clearance, blood sampling from anywhere but the pulmonary artery leads to incorrect conclusions. If pulmonary clearance also occurs in man, as seems likely, then the results of pharmacokinetic studies of chlormethiazole performed to date are in error, since these have not been based on pulmonary artery sampling (Moore et al., 1975; Nation et al., 1976; Jostell et al., 1978; Scott et al., 1980; Seow, Mather and Roberts, 1981; Seow et al., 1981). Halothane anaesthesia abolished the pulmonary clearance of chlormethiazole in these studies. Halothane, enflurane and isoflurane have been shown to inhibit pulmonary clearance of other amines (Hede and Post, 1981; Cook and Brandom, 1982).

In previous studies it was noted that there were significant differences between total body and summed hepatosplanchnic, pulmonary and renal clearances of pethidine in the sheep and, possibly, in other species as well (Mather et al., 1986). This was also the case for chlormethiazole in these studies, although the magnitude of the difference was less for chlormethiazole than pethidine. Errors caused by the loss of chlormethiazole as a result of sampling and assay were considered and excluded on the basis of *in vitro* studies (Upton, Runciman and Mather, 1984). However 20–30% loss of chlormethiazole into the plastic of administration sets has been noted (Runciman et al., 1981) and this imposes an appreciable dose error which registers in the calculation of total body clearance. Studies in progress have confirmed that significant extravisceral clearance or high affinity tissue binding, or both, do occur in the sheep, and that this would contribute to the discrepancies noted in this study.

Thus, in summary, the infusion of chlormethiazole to subanaesthetic blood concentrations caused no haemodynamic changes, and did not alter the kinetics of iodohippurate used in tracer doses to determine blood flow. In addition to decreasing cardiac output, renal and hepatic blood flows, general anaesthesia with halothane decreased the extraction and clearance of chlormethiazole by the liver and abolished the extraction and clearance by lung and kidney, thus adding to the increasing list of metabolic sequelae of halothane anaesthesia. In contrast, high subarachnoid anaesthesia with amethocaine did not alter haemodynamic variables, or the kinetics of chlormethiazole.

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PLACEMENT OF DOUBLE-LUMEN ENDOBRONCHIAL TUBES

Correlation Between Clinical Impressions and Bronchoscopic Findings

G. B. SMITH, N. P. HIRSCH AND J. EHRENWERTH

SUMMARY

Double-lumen endobronchial tubes were placed "blindly" in 23 patients undergoing thoracotomy. Clinical criteria suggested satisfactory positioning in all cases; however, subsequent fibreoptic bronchoscopy revealed malposition in 48%. Bronchoscopic findings included the inability to view the bronchial cuff, narrowing of the bronchial lumen of the tube at the level of the cuff and herniation of the cuff over the carina. The potential hazards associated with these findings are discussed.

Accurate placement of double-lumen endobronchial tubes is essential for optimal gas exchange during one-lung anaesthesia. Until the availability of suitable fibreoptic endoscopes, confirmation of the correct positioning of these tubes was achieved by observing the expansion of the chest and by auscultation. Since then, several reports have advocated the use of the fibreoptic endoscope as an "introducer" over which the double-lumen tube is advanced under direct vision (Shinnick and Freedman, 1982; Ovassapian, Braunschweig and Joshi, 1983). The fibreoptic endoscope has also been used to verify the position of tubes placed "blindly" (Benumof, 1984). In the present study, we have examined the correlation between the clinical signs commonly used to verify the position of double-lumen tubes and the subsequent findings at bronchoscopy.

PATIENTS AND METHODS

Twenty-three consecutive patients undergoing elective thoracotomy which required the use of double-lumen endobronchial tubes were studied. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and neuromuscular blockade produced with suxamethonium 1 mg kg^{-1}. Following laryngoscopy, an appropriately sized double-lumen tube (Bronchocath, National Catheter Company, U.S.A.) was inserted in a "blind" fashion. The tracheal and bronchial cuffs were inflated using one of two techniques, the choice being dictated by the clinical practice of the anaesthetist concerned.

Technique 1. Following inflation of the tracheal cuff, bilateral lung expansion was confirmed by inspection of the movement of the chest wall and by auscultation. The tracheal limb of the catheter mount was then clamped and the tracheal lumen opened to air. Ventilation continued through the bronchial limb of the endobronchial tube and air was introduced to the endobronchial cuff until the reflux of gas from the tracheal limb ceased. The tracheal catheter mount was then unclamped, the tracheal limb reconnected and the ability to inflate both lungs was reconfirmed.

Technique 2. Following intubation both cuffs were inflated with air using the technique described by Brodsky and Mark (1983). No attempt was made to listen for leaks from around the endobronchial limb. Between 1 and 3 ml of air was introduced to the bronchial cuff.

The ability to isolate each lung was then assessed before and after positioning the patient by alternately clamping the tracheal and bronchial limbs and noting the presence or absence of chest

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G. B. SMITH*, B.M., F.F.A.R.C.S.; N. P. HIRSCH, M.B., B.S., F.F.A.R.C.S.; J. EHRENWERTH, M.D.; Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, U.S.A.

*Present address, for correspondence: 5 The Mews, Rownhams, Southampton SO1 8DY.

TABLE I. *Characteristics (mean ± SD) of 23 patients (12 male) studied*

Age (yr)	55.3 ± 15.6
Weight (kg)	71.0 ± 15.2
Height (cm)	172.9 ± 12.2

movement in three areas of each hemithorax: apical, anterior and axilla. Auscultation was performed over these areas. Finally, the presence of moistened exhaled breath in the transparent catheter mount of each limb of the tube was noted.

With the patient in the lateral position, fibreoptic bronchoscopy was performed to determine whether the bronchoscopic findings confirmed the clinical impressions of successful placement of the tube. The fibreoptic endoscope (Machida ENT 4L-50) was first introduced to the tracheal lumen of the tube. The tube was considered to be placed accurately when all of the following were observed:

(1) Unobstructed view of the tracheal carina and the absence of herniation of the bronchial cuff over the carinal surface.

(2) Unobstructed view down the non-intubated bronchus.

(3) Visualization of the bronchial cuff, immediately below the carina.

The fibreoptic endoscope was then introduced to the bronchial lumen of the tube and the following sought:

(1) The absence of constriction of the bronchial limb of the tube at the level of the bronchial cuff.

(2) Unobstructed view of the distal bronchial tree.

RESULTS

The demographic data concerning the 23 patients studied are presented in table I. Nine patients underwent right thoracotomy and 14 a left thoracotomy. In all but one patient, a left-sided Bronchocath was inserted, the exception being a patient with a vascular tumour in the left main bronchus. Eight of the men studied received a 39-French gauge tube and the remainder, a 37-French gauge tube. Of the women, eight were intubated with a 37-French gauge tube and the rest with a 35-French guage. The cuffs of 15 tubes were inflated using technique 1 and eight using technique 2.

In all cases studied, selective isolation of each lung was possible. In all 23 patients, chest expansion was considered satisfactory and equal in the three areas of the chest previously described. Similarly, breath sounds in these areas suggested that ventilation to all lobes of the lungs was adequate. Moisture from exhaled breath was noted in the bronchial and tracheal lumen of the tubes in all cases.

TABLE II. *Bronchoscopic findings*

	No.	%
Observations through tracheal lumen		
Carina visible	19	82.6
Clear view of non-intubated bronchus	19	82.6
Visualization of upper surface of bronchial cuff, immediately below carinal surface	17	73.9
Observations through bronchial lumen		
Constriction of bronchial tube lumen at level of bronchial cuff	1	4.3
View of distal bronchial tree	23	100

Bronchoscopic findings are described in table II. In 11 of the patients (48%), bronchoscopy revealed the double-lumen tube to be in a less than satisfactory position. In four patients (17%), herniation of the bronchial cuff over the carina had occurred. In six patients (26%) the bronchial cuff could not be visualized and in one patient (4%) narrowing of the bronchial lumen of the double-lumen tube was observed.

DISCUSSION

When the Robertshaw double-lumen tube is used, misplacement occurs in approximately 25% of cases (Read, Friday and Eason, 1977). Burton and colleagues (1981) reported a much lower incidence (4%) when the newer p.v.c. double-lumen tubes were used. However, neither of these groups confirmed correct positioning with bronchoscopy.

In the present study, using chest expansion and auscultation as indicators of correct placement of the tube, we found that positioning was satisfactory in all 23 patients. However, using the criteria described, bronchoscopy revealed that in only 52% was the position optimal (fig. 1). In 26% of the patients, we were unable to visualize the bronchial cuff when looking down the tracheal lumen of tube. Using our criteria, the endobronchial limb had been advanced too far beyond the carina. In four out of six of those cases, no clinical sequelae occurred; however, in two, it became apparent at thoracotomy that the left upper lobe was not being ventilated. In each

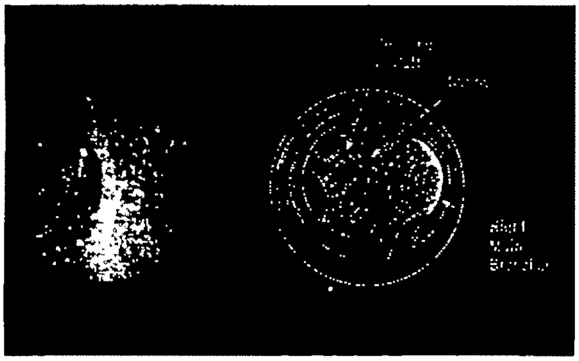

FIG. 1. Left: View through fibreoptic endoscope demonstrating correct position of bronchial cuff lying below the carina. Right: artist's impression of view.

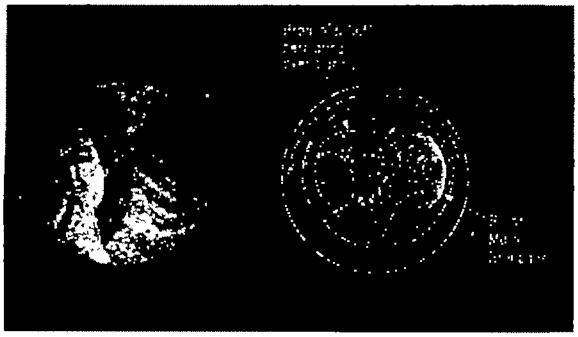

FIG. 2. Left: View through fibreoptic endoscope showing herniation of bronchial cuff over the carina. Right: artist's impression of view.

patient, withdrawing the tube by 1 cm under direct bronchoscopic control resulted in the immediate return of ventilation to that lobe and allowed visualization of the endobranchial cuff. It is interesting to note that, in both patients, breath sounds on the side concerned were considered satisfactory, even over the axilla where it is suggested one is less likely to hear transmitted breath sounds (Benumof, 1983). In the examples cited, the lack of ventilation to the left upper lobe was detected only at thoracotomy and detection would have been unlikely if a right thoracotomy had been performed. The only sign in this instance might have been hypoxia, for which there are many causes.

It is well known that right upper lobe obstruction may occur using a right-sided endobronchial tube, and this has resulted in the increased use of left-sided tubes (Alfrey and Benumof, 1981) even when a left thoracotomy is performed. The cases described illustrate that left upper lobe obstruction may occur with a left endobronchial tube, and this is supported by a recent publication (Brodsky, Shulman and Mark, 1985) which reported two similar cases. With a malpositioned left-sided endobronchial tube, there may be three clinical consequences: failure to ventilate the left upper lobe, failure of the left upper lobe to collapse, or continued ventilation of the left lung when right-sided, one-lung ventilation is planned.

In 17% of the patients studied, herniation of the bronchial cuff over the carina was found to be present (fig. 2). Once again, this complication was not detected using clinical signs. No untoward sequelae occurred, but such malplacement may, under certain circumstances, lead to a number of problems. First, the endobronchial limb may slip out of its bronchus, especially during the positioning of the patient (Saito, Dohi and Naito, 1985). Herniation may also result in obstruction of the unintubated bronchus, making it difficult or impossible to ventilate that lung. Finally, it may prevent the escape of air from the unintubated lung when one-lung anaesthesia is attempted.

The final abnormality that was detected at bronchoscopy was narrowing of the lumen of the endobronchial tube by the endobronchial cuff. Clearly, this is a complication of the introduction of an inappropriately large volume of air to the cuff. Narrowing occurred in only one patient (4%), and it is interesting to note that in this patient the tube was placed and the cuffs inflated using technique 2. This method involves the introduction of a relatively fixed amount of air to the bronchial cuff. We feel that, when using endobronchial tubes, only the minimum volume of air necessary to seal leaks around the tube should be introduced to the cuff. Not only will this prevent the narrowing of the bronchial limb and the consequent increase in resistance to gas flow, it will also minimize the risk of herniation of the cuff and rupture of the bronchus.

Although moist exhaled breath was visible in each limb of the catheter mount in all of the patients studied, it is obvious that this sign will merely indicate that each limb is unobstructed; it does not signify correct placement of the tube.

In conclusion, clinical observations are still used to determine the accurate placement of double-lumen tubes and will detect gross malposition. However, this study suggests that such observations are unreliable signs of the exact position of the bronchial cuff, the presence of herniation of the cuff over the carina or overdistension of the cuff leading to narrowing of the lumen of the tube. We feel that fibreoptic bronchoscopy allows accurate confirmation of the position of double-lumen endobronchial tubes and facilitates repositioning of a malplaced tube. We recommend its use whenever double-lumen tubes are used.

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PULMONARY INJURY INDUCED WITH HYDROCHLORIC ACID: EFFECT OF PRIOR ADMINISTRATION OF RANITIDINE

D. ROYSTON, S. BRAUDE*, K. B. NOLOP* AND S. SAPSED-BYRNE
Departments of Anaesthesia and Respiratory Medicine, Royal Postgraduate Medical School, London

Aspiration of acid gastric contents is associated with acute oedematous lung injury. There is no published evidence of any universally effective treatment for this type of lung pathology. Nonetheless, previous studies have shown that the concentration of histamine was increased in pulmonary oedema fluid following acid injury (Glauser, Millen and Falls, 1979); and that histamine-induced changes in pulmonary solute flux were prevented by prior administration of ranitidine (Braude et al., 1984).

The present study investigated the effect of pretreatment with ranitidine on acid-induced lung injury. Indices of injury used were clearance of ^{99m}TcDTPA as an index of pulmonary solute flux; and the ratio of lung wet weight to lung dry weight as an index of lung water accumulation and pulmonary oedema.

Studies were conducted in anaesthetized, intubated, ventilated specific pathogen free Sprague–Dawley rats (weight 190–276 g) (Minty and Royston, 1985). Injury was induced with intratracheal (i.t.) instillation of hydrochloric acid 1 ml kg^{-1}, pH 2. Control animals received i.t. saline. Acid animals were pretreated with saline or ranitidine 2.5 mg kg^{-1} (LoR) and 25 mg kg^{-1} (HiR) 30 min before i.t. acid. Anaesthesia and ventilation were continued for 4 h after i.t. acid, and the clearance of ^{99m}TcDTPA (expressed as % decline in activity per min) was then measured. The lungs were removed and the wet weight to dry weight ratio (*W:D*) measured. Results (mean (SEM) are shown in table I

TABLE I. *Clearance of* ^{99m}*DPTA and* W:D *ratio.* **P < *0.01 cf control;* ††P < *0.01,* †P < *0.05 cf acid only*

	Control	Acid	Acid LoR	Acid HiR
^{99m}TcDPTA	0.77	4.65**	4.2**	1.12††
clearance	(0.06)	(0.55)	(0.8)	(0.13)
W:D ratio	5.44	6.4**	6.5**	5.8†
	(0.17)	(0.3)	(0.7)	(0.2)
n	18	14	6	12

These studies suggest that histamine plays some part in modulating the pulmonary inflammatory response to direct acid injury; and that ranitidine in high doses reduces significantly the abnormal solute and water flux induced by acid injury.

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EFFECT OF ANXIETY ON GASTRIC EMPTYING IN PREOPERATIVE PATIENTS

K. H. SIMPSON AND A. STAKES*
University Department of Anaesthesia, St James's University Hospital, Leeds

Anxiety is an emotional response to a threatening situation, and can be assessed using questionnaires. The State Trait Anxiety Inventory (STAI), developed to provide a reproducible, self-reporting measure of state and trait anxiety, has been validated against other assessments of anxiety in response to stress (Spielberger, Gorsuch and Lushene, 1970). Anxiety trait (AT) represents the stable predisposition to respond to stress with anxiety. Anxiety state (AS) represents the current subjective feeling of apprehension. The present study was designed to measure gastric emptying before operation and to correlate it with STAI scores.

Thirty fit patients awaiting elective minor gynaecological surgery completed an STAI on the morning of operation. Gastric emptying was measured using paracetamol absorption (Heading et al., 1973). After a fast of at least 4 h, paracetamol 1.5 g was given orally and venous blood samples were taken at intervals for 120 min. Plasma paracetamol concentrations were measured using an enzymatic method (Cambridge Life Sciences). Data were analysed using analysis of variance or Student's *t* test for independent samples.

Anxiety state and anxiety trait were not significantly

TABLE II. *Plasma paracetamol concentrations* ($\mu g\ ml^{-1}$) (*mean* (*SEM*))

	Time (min)						
	15	30	45	60	75	90	120
AS < AT	23.6	26.8	24.3	22.0	20.3	18.7	14.8
($n = 16$)	(5.6)	(3.0)	(1.7)	(1.0)	(0.9)	(1.0)	(0.7)
AS > AT	7.4	13.8	17.2	17.7	17.5	17.2	15.2
($n = 14$)	(2.4)	(2.8)	(2.2)	(1.7)	(1.4)	(1.2)	(1.3)
P	< 0.01	< 0.01	< 0.05	< 0.05	ns	ns	ns

correlated ($r = 0.31$; $P > 0.05$). Multiple regression analysis showed a relationship between AS, AT and indicators of gastric emptying such as peak paracetamol concentration and area under the paracetamol concentration–time curve. Results of the analysis showed that gastric emptying was delayed in patients with low AT and high AS scores. Patients were therefore grouped according to the relationship between their AT and AS scores. Mean plasma paracetamol concentrations were significantly lower at 15, 30, 45 and 60 min in patients with high AS relative to AT scores (table II). These patients also had significantly lower and delayed mean peak paracetamol concentrations ($P < 0.005$) with smaller mean areas under the paracetamol concentration–time curve ($P < 0.005$).

It was concluded that patients with low trait anxiety who develop high state anxiety before operation show delayed gastric emptying.

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LOSS OF RANITIDINE DURING CONTINUOUS HAEMOFILTRATION

E. M. M. POLLOCK*, J. R. DOUGALL*, C. BRYCE*, M. McINTOSH*, P. G. M. WALLACE* AND M. HALLWORTH*
Intensive Therapy Unit and Department of Biochemistry, Western Infirmary, Glasgow

Ranitidine (Zantac) is given frequently to patients in the Intensive Therapy Unit as prophylaxis against peptic ulceration. Patients who are undergoing continuous haemofiltration may lose ranitidine as the molecular size of this drug is considerably smaller than the pore size of the filtration system. Consequently the plasma concentration of ranitidine may decrease. The aim of this study was to assess the loss of ranitidine during haemofiltration.

Ten anuric patients undergoing routine continuous arterio-venous haemofiltration with the Amicon system were studied on days when haemodialysis was not performed. Each patient received ranitidine 50 mg i.v. 8-hourly and the rate of haemofiltration was varied between 150 and 570 ml h^{-1} according to the patient's clinical condition.

In all patients arterial blood was sampled just before i.v. drug administration and then at 5, 20, 40, 60, 105, 210 and 330 min after drug administration. In four patients, haemofiltrate was simultaneously sampled directly from the filter exit port and in six patients a sample of haemofiltrate from the total volume collected over 8 h was analysed.

Plasma and haemofiltrate were stored at −20 °C before extraction with dichloromethane and analysis by HPLC with detection at 320 nm. This assay has a sensitivity of 30 ng ml^{-1} and a coefficient of variation of 16% on repeat sampling.

Comparison of paired plasma and haemofiltrate drug concentrations in four patients suggest that ranitidine filters freely across the membrane of the Amicon. It is calculated that 2.1% (SD 1.4%), (range 0.9–3.9%) of the administered drug mass is lost during 8 h of haemofiltration.

GASTRIC EMPTYING IN POST-PARTUM PATIENTS

M. MILLER*, K. H. SIMPSON AND A. STAKES*
University Department of Anaesthesia, University of Leeds

Gastric emptying may be delayed during labour (Davison, Davison and Hay, 1970). The present study was designed to compare gastric emptying in women during the first 5 days post-partum with that of non-pregnant controls.

Twelve women who were 36–110 h after delivery, awaiting tubal ligation, and 14 non-pregnant women scheduled to undergo minor gynaecological surgery were studied. Gastric emptying was assessed on the morning of operation from the rate of paracetamol absorption (Heading et al., 1973). After fasting for at least 4 h, patients were given paracetamol 1.5 g orally and venous blood samples were withdrawn at intervals for 120 min. Plasma paracetamol concentrations were measured using an enzymatic method (Cambridge Life Sciences). Data were analysed using analysis of variance or Student's *t* test for independent samples.

Post-partum patients were heavier than controls; however, there was no significant difference in age or duration of fasting between the two groups. Post-partum patients had lower mean plasma paracetamol concentrations than controls at 45, 60 and 90 min (table III). Post-partum patients had significantly lower mean peak paracetamol concentrations ($P < 0.05$) and a smaller mean area under the paracetamol concentration–time curve ($P < 0.01$) compared with controls.

TABLE III. *Plasma paracetamol concentrations* ($\mu g\ ml^{-1}$) (*mean* (*SEM*))

	Time (min)					
	15	30	45	60	90	120
Controls	19.5	24.6	24.0	22.2	19.8	14.8
($n = 14$)	(5.8)	(4.1)	(2.4)	(1.5)	(0.9)	(1.3)
Post-partum	14.0	18.7	15.7	15.2	14.6	11.8
($n = 12$)	(3.2)	(3.2)	(2.1)	(2.0)	(2.0)	(2.2)
P	ns	ns	< 0.05	< 0.01	< 0.05	ns

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ATTENUATION BY ALFENTANIL OF THE SYMPATHOADRENAL RESPONSE TO INTUBATION OF THE TRACHEA

D. CRAWFORD*, D. FELL AND G. SMITH
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

Tracheal intubation is associated with pronounced cardiovascular pressor responses and a measurable increase in plasma catecholamines (Derbyshire et al., 1983). The haemodynamic response can be attentuated by alfentanil $15\ \mu g\ kg^{-1}$ and prevented by $30\ \mu g\ kg^{-1}$ (Black, Kay and Healy, 1984). We set out to determine if alfentanil would influence the catecholamine in addition to the pressor response to intubation by measurement of noradrenaline (NA) and adrenaline (Ad) concentrations in arterial blood samples. Following ethics committee approval, 44 patients gave informed consent to the study. Arterial monitoring was instituted under local anaesthesia before induction of anaesthesia with thiopentone followed by 70% nitrous oxide in oxygen. Vecuronium $0.1\ mg\ kg^{-1}$ and alfentanil $10\ \mu g\ kg^{-1}$ (A10), alfentanil $40\ \mu g\ kg^{-1}$ (A40), or saline were given. Systolic and diastolic arterial pressures were recorded and ECG displayed. Arterial blood samples (10 ml) were taken for catecholamine analysis before induction, immediately before laryngoscopy and at 1, 3 and 5 min after tracheal intubation. There were no differences between the groups in the dose of thiopentone (3–5 $mg\ kg^{-1}$).

Mean arterial pressures (MAP) are shown in table IV.

TABLE IV. *Mean arterial pressures (mm Hg) (mean (SEM)).* $P < 0.05$: **within groups; †compared with saline; ‡compared with A10*

	Before ind.	Before laryng.	Time after intubation (min) 1	3	5
Saline	101 (4)	103 (9)	131 (7)*	117 (8)*	102 (8)
A10	109 (5)	74 (4)*†	103 (6)†	95 (6)*	91 (6)*
A40	104 (5)	68 (5)*†	59 (5)*†‡	61 (5)*†‡	61 (4)*†‡

In the A40 group, 11 of the 15 patients received an i.v. infusion of more than 750 ml of fluid to maintain arterial pressure. In the control group plasma catecholamine concentrations increased and decreased with a pattern similar to that previously reported (Derbyshire et al., 1983). The A10 group demonstrated a significant increase in NA from postinduction to 3 min after intubation ($P < 0.01$), but no change in Ad concentrations. In the A40 group both Ad and NA decreased significantly after intubation ($P < 0.05$).

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CEREBRAL EXTRACELLULAR FLUID ION ACTIVITIES AND PATHOLOGICAL EFFECTS OF HYPOTENSION IN CATS

D. WEIR*, D. I. GRAHAM* AND C. S. GOODCHILD*
University of Leeds Department of Anaesthesia and The Institute of Neurological Sciences, Southern General Hospital, Glasgow

Morris and others (1983) established a model of global partial cerebral oligaemia in anaesthetized cats producing characteristic changes in cerebral extracellular fluid (ECF), potassium ion activity (K^+_e) and hydrogen ion activity (pH_e) with some restitution towards control values during a recovery period. The present investigation was designed to examine the relationship between these changes and the extent of neuropathological damage.

Triple-barrelled ion-sensitive electrodes inserted to a depth of 0.5–1.0 mm in the left middle suprasylvian gyrus of nine male cats were used to measure K^+_e (in nine cats), Ca^{2+}_e (in seven) and pH_e (in seven). Maintenance anaesthesia was 0.7% halothane in 50% nitrous oxide in oxygen. Ventilation was adjusted to maintain Pa_{CO_2} in the range 3.5–4.0 kPa. Mean arterial pressure (AP) was measured continuously and, following control measurements was reduced to 30 mm Hg for 30 min by infusing trimetaphan camsylate (TMP) at a rate not exceeding $10\ mg\ kg^{-1}\ h^{-1}$ combined with blood withdrawal if necessary. Mean AP was restored to not less than 60 mm Hg by cessation of TMP infusion, re-infusion of blood and if necessary the infusion of dopamine at a maximum rate of $20\ \mu g\ kg^{-1}\ min^{-1}$ for a recovery period of 120 min. Maintenance anaesthesia was continued while perfusion–fixation was carried out to permit subsequent neuropathological assessment.

Maximum K^+_e and minimum Ca^{2+}_e and pH_e were noted, as were ECF ion activities at 50 and 100 min of recovery. The Spearman rank correlation coefficient was used to compare ion measurements and the severity of pathological damage as shown in table V.

The observed pattern of changes of ionic activities is similar to those previously described in this model (Morris et al., 1983) with the addition of the measurement of Ca^{2+}_e. An investigation of the neuropathological effects of diffuse cerebral ischaemia in the cat (Ginsberg et al., 1979) produced lesions of a disposition similar to those in this study and it was suggested that the pathological consequences of 30 min of cerebral ischaemia evolved during the post-ischaemic period. In the present study the derangement of all ECF ion activities

TABLE V. *Correlations of ionic activities and severity of pathological damage*

	K^+_{max}	K^+_{50}	K^+_{100}	Ca^{2+}_{min}	Ca^{2+}_{50}	Ca^{2+}_{100}	pH_{min}	pH_{50}	pH_{100}
r_s	0.733	0.671	0.75	0.133	0.366	0.40	0.116	0.42	0.598
P	0.05	ns	0.05	ns	ns	ns	ns	ns	ns

was most closely correlated with neuropathological damage at 100 min of recovery although only the value for K^+_e reached statistical significance. It would appear that K^+_e during the late recovery period following partial global cerebral oligaemia provides an index of neuropathological damage.

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CEREBROSPINAL FLUID AND PLASMA MORPHINE CONCENTRATIONS AFTER ORAL (MST) AND I.M. MORPHINE

L. P. CLAFFEY* AND W. P. BLUNNIE*
Department of Anaesthesia, Mater Misericordiae Hospital, Dublin

The efficacy of opioid analgesia may be related to the existence of significant amounts of drug at the central nervous system receptors which have been shown to be particularly plentiful in the substantia gelatinosa (Pert and Synder, 1973). We have measured plasma and cerebrospinal fluid (CSF) morphine concentrations after oral morphine sulphate tablets (MST) and i.m. morphine administration in patients undergoing transurethral resection of the prostate under subarachnoid anaesthesia. Efficacy as premedication and postoperative analgesia was also assessed.

Hospital Ethical Committee and National Drugs Advisory Board approval were obtained, as was each patient's informed consent to participate in the study. Thirty patients were allocated to one of two groups. Group I received MST 30 mg by mouth 2 h before operation. Group II received morphine sulphate 10 mg i.m. 1 h before operation. Blood and CSF were sampled in the anaesthetic room before administration of spinal anaesthesia. The samples were analysed by the Nuffield Department of Clinical Biochemistry, Oxford, using radioimmunoassay.

The groups were similar in age and weight. There was a wider scatter of plasma morphine concentrations after MST than after i.m. administration. CSF concentrations were higher in the i.m. group. The Mann-Whitney *U* test was applied to both sets of values.

The higher plasma morphine concentrations in the MST group were significant at a *P* value of less than 0.05. The higher CSF values in the i.m. group proved significant at a *P* value of less than 0.01. Clinically, there was no significant difference between the two groups from the point of view of premedication and postoperative analgesia.

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INTRATHECAL MIDAZOLAM AND THE STRESS RESPONSE TO UPPER ABDOMINAL SURGERY

T. P. CRIPPS* AND C. S. GOODCHILD*
University of Leeds, Department of Anaesthesia

Midazolam (Hypnovel, Roche), a water soluble imidazobenzodiazepine, was reported by Rigoli (1983) to cause analgesia when given extradurally in humans. Whitwam and others (1982) showed that intrathecal midazolam depressed somatosympathetic reflexes in dogs, an effect which was reversed by benzodiazepine receptor antagonists; this effect is probably the result of interference with transmission of nociceptive information in the dorsal horn. We have studied the effect of this drug given intrathecally on the metabolic and stress response to surgery.

Fourteen patients undergoing elective upper abdominal surgery were studied: eight received intrathecal midazolam 2 mg and six were controls. They were anaesthetized according to a rigid procedure. Premedication was midazolam 5–10 mg i.m. Anaesthesia was induced with thiopentone 4 mg kg^{-1} followed by alcuronium 0.3–0.4 mg and maintained by ventilation of the lungs (V_T 10 ml kg^{-1}; $f = 10$ b.p.m.) with nitrous oxide, oxygen and 0.4% enflurane. Peroperative arterial pressure (AP) and heart rate were recorded. If the AP was increased above control or there was clinical evidence of inadequate anaesthesia, the inspired enflurane concentration was increased at 5-min intervals to 0.8%, and then to 1.0% and thereafter diamorphine 1 mg was administered every 5 min until an adequate depth of anaesthesia was attained. Blood was taken from a central venous line for analysis of glucose, pyruvate, lactate and cortisol concentrations immediately before induction of anaesthesia and at 20, 40, 60, 120, 240 and 360 min after skin incision. Peroperative and postoperative opiate consumption were also recorded.

Patients were similar in age, weight, sex distribution and peroperative systolic AP. None of the midazolam group required peroperative opiates, while all the control patients did ($P = 0.0003$, Fischer's exact test). Despite this, enflurane consumption, postoperative analgesic requirements and the smoothness of anaesthesia did not differ significantly (table VI).

TABLE VI. *Results (mean ± SD). *P = 0.0003*

	Control ($n = 6$)	Midazolam ($n = 8$)
Systolic AP (mm Hg)		
Preoperative	129 (19)	114 (16)
Peroperative	134 (16)	121 (19)
Coefficient of variation of peroperative AP (%)	11 (4.7)	7 (2.5)
Heart rate perop. (beat min^{-1})	87 (13)	88 (14)
Coefficient of variation (%)	11 (4.2)	7 (3.5)
Enflurane consumption index (%)	0.82 (0.16)	0.64 (0.29)
Analgesia needed perop. (No. patients)	6*	0*
First postop. dose (min)	30 (27)	121 (133)

There was no significant change of pyruvate and lactate concentrations between groups or in response to surgery. Blood glucose and cortisol concentrations significantly increased above control, but there was no difference between the groups.

We conclude that intrathecal midazolam provides a measure of intraoperative analgesia similar to that with i.v. diamorphine, but that it does not affect the concentrations of metabolites measured.

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AWARENESS DURING BRONCHOSCOPY: EVALUATION OF A RANDOM NOISE GENERATOR

J. K. MOORE* AND A. H. SEYMOUR*
Department of Anaesthesia, Royal Infirmary, Glasgow

We have studied the incidence of awareness during bronchoscopy and evaluated the effectiveness of auditory random noise in preventing awareness. We studied 104 unpremedicated patients undergoing elective bronchoscopy. I.v. atropine, thiopentone and suxamethonium were used to induce anaesthesia. Once asleep, all patients were connected to the random noise generator. Fifty-two patients received random noise. Oxygen was delivered by venturi ventilation and anaesthesia maintained with increments of thiopentone and suxamethonium. The anaesthetist recorded the drugs given, duration of procedure, time to response to command and any suspicion of awareness. Patients were interviewed 6 h after operation and the incidence of awareness and dreaming assessed. One patient who received random noise was lost to follow-up. The two groups were comparable with respect to age, sex and thiopentone dose (mg kg^{-1} min^{-1}).

Random noise. Three patients reported awareness, none with pain. No patient reported dreams. The anaesthetist suspected awareness in 10 patients of whom only one was actually aware.

Control group. Four patients reported awareness, three with pain. A further four patients reported dreams. In two of these patients the dreams were unpleasant. Awareness was suspected in four patients; one of these was actually aware and one had pleasant dreams.

Awareness was not related to the age or sex of the patient, or to the dose of thiopentone. No awareness occurred when the procedure lasted less than 5 min. Awareness was associated with a short time interval between removal of the bronchoscope and response to command.

Patients under anaesthesia can hear, and auditory events are registered by the association cortex. Despite postanaesthetic verbal amnesia, Bennett, Davis and Giannini (1985) demonstrated non-verbal behaviour indicating learning of intraoperative spoken suggestion. Cherkin and Harroun (1971) suggested that unpleasant recall may occur when a light level of anaesthesia coincides with acute pain or with auditory stimuli of directly threatening or emotional content. In this study, when random noise was applied only one of the 10 patients whom the anaesthetist suspected of being aware was actually aware, compared with two out of four patients in the control group. This may suggest that more instances of awareness would have been recorded had random noise not been given. The use of a random noise generator to flood the remaining vestiges of sensory perception may create a higher threshold to awareness.

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EFFECTS OF pH CHANGES ON THE ACTION OF DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

S. M. M. MURPHY*, A. M. WILSON AND
D. P. O'MAHONY*
Department of Pharmacology, University College, Cork

Changes in pH are known to influence the actions of neuromuscular blocking agents. Both non-depolarizing agents and depolarizing agents have been studied *in vivo* and *in vitro*. In published work results have varied. It seems probable that some of the inconsistencies have been the result of the use of different species and techniques. In this study three depolarizing agents were examined for the effects of pH changes on their action, using, for each drug, the same preparation and the same experimental procedure. Suxamethonium and decamethonium were studied, and also suxethonium; the effects of pH changes on the action of this drug appear not to have been reported previously.

The rat phrenic nerve–diaphragm preparation was used. This was mounted in an organ bath containing Krebs' (double glucose) solution at 36 °C, bubbled with 5% carbon dioxide in oxygen, pH 7.5. Supramaximal stimuli were applied to the nerve and the diaphragm contractions recorded isometrically. The pH of the bath solution was monitored continuously. The pH was decreased to 7.1 by bubbling with 10% carbon dioxide in oxygen and increased to 8.0 by bubbling with oxygen alone. In each experiment the replacement gas was allowed to act for 10 min. At the end of this time 5% carbon dioxide in oxygen was restored. The pH was first changed without the addition of any drug. This was the control. Fifteen minutes later the drug was added. When the resulting block was considered to be as steady as could be achieved, the pH was changed as described above. For each drug, five different hemidiaphragms were used to test the effects of an increase in pH and a second series of five were used to study the effects of decreased pH. In quantifying the effects of a change in pH on the actions of a drug, two factors were taken into consideration: (1) any change induced in twitch height in the control record and (2) the degree of block in the absence of a pH change. This allowed the calculation of an "expected" twitch height which was then compared with the twitch height actually observed. Statistical significance was tested for by paired *t* tests.

Significant antagonism of decamethonium occurred at pH 7.8 and greater, and of suxethonium at pH 8.0. Acidosis produced by increasing carbon dioxide enhanced blockade by decamethonium and suxethonium, but not to a statistically significant degree. Suxamethonium blockade was enhanced by alkalosis and by acidosis; in neither case was statistical significance achieved.

If all three drugs act by similar mechanisms, one might expect their actions to be affected in the same way by changes in pH. This was so for decamethonium and suxamethonium but not for suxamethonium in this study. An explanation for this finding may lie in the chemical structure of suxamethonium.

EFFICACY OF ANTAGONISM OF ATRACURIUM NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE

M. FOX*, S. KEENS* AND J. E. UTTING
University Department of Anaesthesia, Liverpool

There is surprisingly little objective information about either the speed of recovery from neuromuscular blockade with atracurium when neostigmine has been administered or the dose of neostigmine which should be used. In addition, in some circumstances, large doses of neostigmine may increase the degree of fade to tetanic rates of stimulation (50 Hz) (Payne, Hughes and Al Azawi, 1980). An investigation of the reversal of atracurium block seemed to be indicated and the train-of-four (TOF) technique was used, since this gives a good indication of clinical reversal (Ali et al., 1981).

Thirty-eight patients were studied and ethical approval and informed consent obtained. An EMG (Medelec MS6) was used to record action potentials over the thenar eminence from elicited stimulation of the ulnar nerve using the standard TOF at intervals of 12 s. The rates of the first response to control (A′/A) and the fourth to the first (D′/A′) were studied and the times to 70% recovery, either after neostigmine or spontaneously, were noted. Anaesthesia was with thiopentone (for induction), fentanyl, droperidol and nitrous oxide in oxygen, no volatile agents being given. After control measurements, atracurium 0.5 mg kg^{-1} was administered with increments (0.2 mg kg^{-1}) as required. The effect of one dose of neostigmine 2.5 mg and of two doses of 2.5 mg separated by 2 min (timing from first dose) was studied both in "profound" (A′/A approx. 10%) and "moderate" (A′/A approx. 50%) block, as was spontaneous recovery. Student's unpaired *t* test was used to assess significant differences in recovery times.

TABLE VII. *Time to 70% recovery (min) (SD)*

	Spontaneous	Neostigmine	
		2.5 mg	2.5 mg + 2.5 mg
Moderate block			
A′/A	7.3 (2.7)	2.8 (0.6)	2.2 (0.8)
D′/A′	14.3 (6.2)	3.5 (1.2)	3.0 (1.0)
		$n = 9$	$n = 5$
Profound block			
A′/A	25 (9.5)	8.2 (2.9)	7.4 (1.7)
D′/A′	32.3 (10.4)	12 (3.5)	11.2 (2.3)
	$n = 10$	$n = 9$	$n = 5$

Table VII shows that times to 70% recovery after neostigmine (one or two doses) were always faster than during spontaneous recovery ($P < 0.01$ in each case). There was however, no practical difference in the speed of recovery when one or two doses of neostigmine were used. Neostigmine, even in the larger doses, always caused an increase and never a decrease in the speed of recovery of both A′/A and D′/A′.

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SUXAMETHONIUM AND RECOVERY FROM ATRACURIUM

M. M. MOHARIB*, **T. H. CLUTTON-BROCK*** AND A. M. S. BLACK
Sir Humphry Davy Department of Anaesthesia, University of Bristol

Small doses of suxamethonium (25–50 mg) are sometimes given for brief paralysis to aid abdominal closure if the abdomen tightens with recovery from non-depolarizing block. Nowadays, neuromuscular monitoring usually measures the twitch response of a hand muscle. This is usually increased by small doses of suxamethonium given in the early and middle stages of recovery from a non-depolarizer; larger doses are needed to produce paralysis. Critics of the practice assert that large doses of suxamethonium may interact unfavourably with the non-depolarizer, or with an antagonizing agent given too soon after the suxamethonium. Adherents deny that large doses are necessary; a dose of 25–50 mg of suxamethonium usually does relax the abdominal muscles to the surgeon's satisfaction. This has been our experience, even when we warn the surgeons that we may be giving a placebo.

It is difficult to devise a convenient measure of what the surgeons feel, but the diaphragm is an abdominal muscle which exerts readily recordable effects. We devised the following study to indicate the simultaneous effects, on the diaphragm and the hand, of giving suxamethonium 25–50 mg during recovery from atracurium. We studied 10 patients undergoing abdominal operations who had been intubated using atracurium, and whose general anaesthesia was supplemented by extradural blockade and 0.5–1% halothane. We monitored airway pressure from the catheter mount to the endotracheal tube, using a Gould P23 ID transducer, neuromuscular transmission using a Datex relaxograph, and airway $P\text{co}_2$ using a Gould capnograph.

The opioid requirements were minimal, and if the end-tidal $P\text{co}_2$ was kept around 5.5 kPa the patients began to make ventilatory efforts as the atracurium wore off. These were readily seen in the airway pressure trace. The nitrous oxide was switched off and the patient was preoxygenated for 3–4 min using oxygen and halothane, suxamethonium 25–50 mg was flushed in via a fast-flowing infusion, and the artificial ventilation was stopped for 2 min, while the effects on airway pressure fluctuations and neuromuscular responses were recorded. Ventilation was resumed, by which time the end-tidal $P\text{co}_2$ had increased to between 6.5 and 7 kPa. In some patients a further dose of atracurium was given, and the test was repeated when and if suitable conditions recurred during recovery.

The test was undertaken 20 times in the 10 patients. The response of the first dorsal interosseous muscle was always increased, but in 18 tests, there was a concurrent decrease in the fluctuations in airway pressure produced by the diaphragm. In two tests, the effects on the airway pressure were equivocal, but the fluctuations never increased with the increased responses of the first dorsal interosseous muscle.

One should not criticize a practice aimed at abdominal muscles, on the basis of measurements made on hand muscles.

LAUDANOSINE PHARMACOKINETICS AFTER BOLUS ATRACURIUM IN PATIENTS WITH HEPATO-BILIARY DYSFUNCTION

P. VINE*, N. BOHEIMER*, S. WARD,
B. WEATHERLEY*, A. BUICK* AND I. SMITH*
Anaesthetic Department, Kings' College Hospital, London and Wellcome Research Laboratories, Beckenham, Kent

Laudanosine is a principal breakdown product of atracurium following Hofmann degradation. It is eliminated from normal patients at a slower rate than atracurium ($T_{\frac{1}{2}}^{\beta} \simeq 200$ min) and this elimination is not significantly altered in patients without renal function (Boheimer et al., 1985). It is therefore possible that the main organ of elimination is the liver. This study was undertaken to investigate the pharmacokinetic profile of laudanosine in patients with hepato-biliary disorders.

Five patients gave informed consent and each was undergoing major surgery. Each received a single bolus dose of atracurium 0.3–0.4 mg kg^{-1} and serial blood samples were taken up to 500 min in four patients and 1400 min in one. The methods of collection and analysis were as previously described. Further neuromuscular blockade was provided with pancuronium.

Atracurium plasma concentrations were found to be as expected from the doses given. The peak laudanosine concentrations (mean ± SD) were measured at 2 min (0.18 ± 0.08 μg ml^{-1} compared with 0.19 ± 0.04 in normal patients), decreased rapidly by 15 min (to ≃ 0.05 μg ml^{-1}), then decayed slowly. These laudanosine concentrations were treated by non-linear least squares analysis to determine terminal half-lives ($T_{\frac{1}{2}}^{\beta}$) and apparent clearances (Cl_{app}) (table VIII).

TABLE VIII. *Bilirubin (B) (mmol litre^{-1}), γ-glutamyl transpeptidase (γ-GT) (iu litre^{-1}), prothrombin ratio (PR), terminal half-life* ($T_{\frac{1}{2}}^{\beta}$) *(min) and apparent clearance* (Cl_{app}) *(ml min^{-1} kg^{-1})*

Diagnosis	B	γ-GT	PR	$T_{\frac{1}{2}}^{\beta}$	Cl_{app}
Cancer of head of pancreas	279	649	1.0	480	8.0
Cancer of head of pancreas	200	460	1.0	673	4.8
Cancer of head of pancreas	360	81	1.7	4651	0.9
Cancer of head of pancreas	298	1132	1.0	494	11.2
Hepatocellular infiltration	15	1078	1.1	592	1.9

This preliminary study suggests that peak concentrations of laudanosine are similar to those found in normal subjects, but clearances and half-lives are markedly altered in hepatic disease, the amount of change being related to the degree of hepatic dysfunction.

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EFFECT OF VECURONIUM AFTER PANCURONIUM

B. KAY, R. J. CHESTNUT*, J. SUM PING* AND
T. E. J. HEALY
Department of Anaesthesia, University of Manchester

Vecuronium has been used for long surgical procedures by infusion or by intermittent injections. However, such methods of use, although offering the advantage of the fast recovery of muscle action seen after vecuronium, are not economical. It may be that the use of longer-acting pancuronium followed by vecuronium would offer the advantages of economy and rapid recovery. The aim of the present study was to investigate the duration of effect of vecuronium administered after pancuronium.

Fourteen unpremedicated patients requiring prolonged major surgery were given i.v. pancuronium 0.055 mg kg^{-1} (ED$_{95}$) after induction of anaesthesia using thiopentone and fentanyl. The trachea was intubated and ventilation to normocapnia using 70% nitrous oxide in oxygen maintained. Neuromuscular transmission was monitored using a train of four supramaximal stimuli to the ulnar nerve every 20 s, the integrated evoked compound action potential of the adductor pollicis being recorded.

At a clinically appropriate level of recovery of neuromuscular transmission where the response to the first stimulus (T1) was 10–20% of control response, a dose of vecuronium 0.5 mg (five patients) or 0.25 mg (nine patients) was given i.v. The same dose was repeated the next and every subsequent time the same level of response was achieved until recovery was allowed towards the end of surgery.

Four men and 10 women were observed (mean 61.8 kg weight, mean age 45.2 yr). The mean and median T1 after pancuronium was 7% (0–17%); the first dose of vecuronium was given after a mean 23.1 min.

In every case the duration of effect of the first dose of vecuronium was longer than that of subsequent doses. The mean duration of effect of the first dose of vecuronium 0.25 was 10.2 ± 1.1 (SEM) min, longer than that of any subsequent dose, the relation of duration of effect of individual doses to cumulative dose being exponential.

A similar mean duration of effect of vecuronium 0.25 mg, 5.35 min, was observed from the third dose (given at a mean time of 40.6 min after pancuronium) onwards. The first dose, given a mean 23.1 min after pancuronium had a longer duration of effect, the second (at a mean time of 33.3 min after pancuronium) being intermediate in effect.

It appears that interaction between pancuronium and vecuronium initially extends the duration of effect of vecuronium, but that the advantage of a rapid recovery of neuromuscular transmission when vecuronium is used to maintain paralysis after pancuronium becomes apparent as the effect of pancuronium disappears.

ESTIMATION OF VECURONIUM DYNAMICS USING NON-LINEAR SYSTEMS INDENTIFICATION

D. A. LINKENS, M. KHELFA AND A. J. ASBURY†
Department of Control Engineering, University of Sheffield;
†Department of Anaesthesia, Western Infirmary, Glasgow

In a previous paper (Linkens and Asbury, 1985) it was shown that linear pharmacokinetics and non-linear pharmacodynamics of vecuronium could be estimated without recourse to blood sampling. The technique involved a two-stage process involving on-line closed-loop control followed by open-loop pseudo-random binary sequence (PRBS) excitation. Linear and non-linear components were estimated separately using the two-stage data.

In this communication the complete identification is undertaken from data obtained during the initial transient reponse of the system under closed-loop control.

There are two major problems in simultaneous linear and non-linear identification. The first is the need to obtain good conditions of identifiability under closed-loop control, which can be achieved by superimposing an additional PRBS stimulus on the system to give "persistent excitation". The second problem relates to techniques available for non-linear estimation of parameters. There are two main methods available for this difficult problem, each of which has relative advantages and difficulties, and both techniques must be used in identification of neuromuscular blockade. One method estimates a non-linear difference equation (called a NARMAX model) providing a general description of the process, but giving no indication of underlying physiological structure. It can however, be used with short lengths of data and under a variety of signal conditions. For these reasons, this technique is first applied to the experimental vecuronium data under closed-loop control.

The second technique for non-linear identification is based on Volterra kernels (Marmarelis and Marmarelis, 1978) and has the disadvantages of requiring very long data lengths and being applicable only for special types of inputs such as Gaussian white noise. It does, however, give the possibility of detecting and estimating the structure of the system. Thus the NARMAX model obtained from the first stage on the real data can be explored via off-line simulation.

Experimental data were obtained from healthy mongrel dogs using a procedure described in Linkens and Asbury (1985). In the results shown the NARMAX model produced a good fit to the experimental data using a third-order model with a second degree non-linear equation. This was obtained with 240 data points from a smooth sequence originally sampled at 10-s intervals. This model was then simulated on a computer and excited with a 5000-point Gaussian white noise sequence with mean and variance adjusted to suit the operating level of the experimental data. Using cross-correlation techniques, the impulse response of the linear part of the drug dose–response (related to the pharmacokinetics) was estimated. This gave a second-order system with time constants commensurate with results using open-loop experiments. The non-linear static response (related to the pharmacodynamics) could now be estimated via filtered drug data and RIEMG output data. This was fitted to a Hill equation and gave parameters also commensurate with previous results and earlier published work using blood samples and assay techniques.

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FADE PROFILES DURING SPONTANEOUS OFFSET OF NEUROMUSCULAR BLOCKADE: GALLAMINE AND VECURONIUM COMPARED

S. J. POWER*, M. J. DAROWSKI*, W. J. GALLAGHER* AND R. M. JONES
Department of Anaesthetics, United Medical and Dental Schools of Guy's and St Thomas' Hospitals (University of London), London

Neuromuscular blocking drugs are associated with different degrees of train-of-four (TOF) fade during onset of action (Williams, Webb and Calvey, 1980). This has been ascribed to a varying affinity for pre- and post-synaptic receptors (Williams, Webb and Calvey, 1980; Donati, Ferguson and Bevan, 1983). However, the degree of fade occurring during onset of blockade may not be the same as during offset. We have studied the degree of fade during spontaneous offset, as well as onset, for gallamine and vecuronium—agents which are thought to have widely varying degrees of pre- and post-synaptic activity.

Electromyographic monitoring utilized the ulnar nerve at the wrist and the hypothenar muscles for positioning of the stimulating and recording electrodes. A TOF pattern of stimulation with supramaximal 0.1-ms square wave impulses was used, repeated every 20 s. Induction of anaesthesia was with sodium thiopentone 4–6 mg kg^{-1} and fentanyl 1 µg kg^{-1}. Control recordings were obtained, then vecuronium or gallamine was given in approximately equipotent (ED_{95}) doses (0.05 and 2.0 mg kg^{-1}, respectively). Anaesthesia was maintained with oxygen and nitrous oxide (1:2), with 0.5–1.0% inspired halothane and incremental fentanyl. A complete record of twitch height was obtained during onset and spontaneous offset. Only recordings in which T1 returned to within 10% of control T1 were included. Comparisons of TOF fade between blockers were made when the initial twitch had decreased to 25% of control during onset and 25%, 50% and 75% of control during offset. Statistical analysis utilized Wilcoxon's Rank Sum test. Results (table IX) are reported as mean (SD).

TABLE IX. *Results*

	Vecuronium	Gallamine	*P*
n	11	8	
Age (yr)	30 (14)	53 (18)	
Weight (kg)	64 (9)	69 (9)	
Onset T4 ratio when T1 = 25%	0.47 (0.09)	0.13 (0.11)	< 0.01
Offset T4 ratio			
T1 = 25%	0.06 (0.09)	0.04 (0.06)	ns
T1 = 50%	0.12 (0.07)	0.13 (0.06)	ns
T1 = 75%	0.21 (0.08)	0.33 (0.07)	< 0.05
Offset times to T1 50% (min)	18 (3)	98 (50)	

This study confirmed the marked degree of fade associated with gallamine during onset, the value being appreciably greater than that associated with vecuronium. During offset, however, the degree of fade was very similar at values up to T1 = 75%. When T1 had recovered to 75%, gallamine was in fact associated with significantly less fade than vecuronium. These results call into question previous assumptions of the "fade profile" of neuromuscular blocking drugs and hence their likely relative pre- and post-synaptic effects. They also demonstrate that conclusions drawn from results obtained during the onset of blockade cannot be applied during spontaneous offset.

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STUDY OF MORPHINE SULPHATE TABLETS WITH AND WITHOUT METOCLOPRAMIDE

M. W. CODY*, W. P. BLUNNIE* AND A. J. McSHANE
Department of Anaesthesia, Mater Misericordiae Hospital, Dublin

INTRAOPERATIVE FLUIDS—HOW MUCH AND OF WHAT?

I. E. TWEEDIE*, J. N. BAXTER*, G. T. TAYLOR*, S. J. KEENS* AND I. T. CAMPBELL
University Departments of Anaesthesia and Surgery, Royal Liverpool Hospital, Liverpool

It is conventional practice during surgery to maintain AP and urine output by replacing blood loss and infusing crystalloids. Recommendations for fluid regimens vary and there is little objective appraisal of efficacy. The effects on urine output, cardiovascular stability and biochemistry were studied using infusions of 10 or 15 ml kg^{-1} h^{-1} of a high (Hartmann's) or low (5% dextrose or 4% dextrose in 0.18% saline) sodium solution.

Twelve patients (median age 63.5; range 39–77 yr) having intestinal resections consented to participate in the study. Six received 10 ml kg^{-1} h^{-1} of Hartmann's solution ($n = 3$) or 5% dextrose ($n = 3$). Six received 15 ml kg^{-1} h^{-1} of either Hartmann's solution ($n = 3$) or 4% dextrose in 0.18% saline ($n = 3$). For analysis, the dextrose and dextrose in saline groups are considered together. All received 0.18% saline in 4% dextrose 1000 ml during the 1 h before operation. A bolus of para-amino hippurate (PAH) and inulin was given and an infusion started of PAH and inulin, diluted in the fluid to be given during operation at 240 ml h^{-1}. This infusion continued until the end of surgery. After 25 min, urine output was measured for 15 min before and for 15 min after induction of anaesthesia. The operation then started. Intraoperative fluids were started through a separate infusion at a rate calculated to total 10 or 15 ml kg^{-1} h^{-1}, taking into account the 240 ml h^{-1} already being given. Urine output was measured every 30 min of the operation and hourly for 5 h thereafter. Anaesthesia was with thiopentone, morphine, pancuronium, IPPV nitrous oxide, oxygen and 0–1% halothane. Measured blood loss in excess of 600 ml was replaced with blood, counting one unit of blood as 450 ml. The first unit was whole blood and the balance "plasma reduced".

Results were analysed, classifying patients by the type of fluid and volume. All groups were comparable in terms of patient characteristics, blood loss, anaesthetic drug dose, postoperative fluid regimen (0.18% saline in 4% dextrose 1.8 ml kg^{-1} h^{-1}) and duration of surgery.

Two patients who received 10 ml kg^{-1} h^{-1} had to be given extra fluid (Hartmann's solution 1 litre) because of clinically unacceptable hypotension, one during operation, one after operation. Arterial pressure in the 15-ml kg^{-1} group was maintained during operation, but in the 10-ml kg^{-1} group it decreased significantly. The 15-ml kg^{-1} group passed more urine than the 10-ml kg^{-1} group ($P < 0.05$) and the dextrose group more than the Hartmann's group ($P < 0.01$). For the first 90 min median urine output of the Hartmann's group was less than 0.5 ml min^{-1}, but it was greater than 0.5 ml min^{-1} in all other groups at all other times. Patients receiving dextrose became hyponatraemic (Na < 120 mmol litre^{-1}) and hypo-osmolar (< 260 mmol kg^{-1}). Blood-sugar in the dextrose group increased to 23.4 mmol at 120 min, but was normal by the end of the postoperative period.

Crystalloid fluid requirements given in addition to replacement of measured blood loss during major abdominal surgery appear to be in the region of 15 ml kg^{-1} h^{-1}. During operation, dextrose solutions are more effective in promoting urine output than is Hartmann's solution, but they are accompanied by degrees of hyperglycaemia, hyponatraemia and hypo-osmolality that are probably unacceptable.

PROPOFOL AND METHOHEXITONE AS INDUCTION AGENTS FOR DAY-CASE ISOFLURANE ANAESTHESIA

D. P. O'TOOLE*, K. R. MILLIGAN*, J. P. HOWE*, J. S. C. McCOLUM* AND J. W. DUNDEE
Department of Anaesthetics, The Queen's University of Belfast and Mater Infirmorium Hospital, Belfast

Rutter and colleagues (1980) have suggested that recovery from anaesthesia with propofol is similar to that from methohexitone. However, a recent study (Mackenzie and Grant, 1985) with enflurane maintenance has shown propofol to have better recovery characteristics than methohexitone. The present study compared the induction and recovery characteristics of equivalent doses of propofol and methohexitone given as induction agents, before nitrous oxide in oxygen and isoflurane anaesthesia.

Fifty healthy unpremedicated patients, aged 16–55 yr, undergoing minor gynaecological procedures were randomly allocated to receive one or other induction agent. Both groups were broadly comparable with respect to age, weight and duration of anaesthesia. Doses were propofol 2.5 mg kg^{-1} and methohexitone 1.5 mg kg^{-1} given over 20 s into a peripheral vein. Maintenance was with 3% isoflurane initially, reducing to 1–1.5%.

A second anaesthetist, unaware of the agent, assessed recovery using both clinical criteria and psychomotor testing. The former included time to opening eyes, orientation and giving correct date of birth as well as an assessment of alertness and gait at 20, 40 and 60 min after operation. Four "choice reaction time" tests (CRT) (Wilkinson and Houghton, 1975) were performed at 20, 40 and 60 min after operation and compared with preoperative values in both groups. An identical test was undertaken by a control group ($n = 25$) not undergoing anaesthesia.

Results (table X) were analysed statistically using the Mann–Whitney U test, independent t test analysis of variance, χ^2 and Fischer's exact probability tests where appropriate.

TABLE X. *Mean ± SEM changes (ms) from baseline CRT values after propofol (P), methohexitone (M) and no treatment (C)*

Time (min)	P	M	C
20	30±15	102±80	−80±16
40	−41±16	−31±18	−143±27
60	−76±16	−70±14	−165±29

Induction with propofol was significantly smoother ($P < 0.01$), but was associated with greater cardiovascular and respiratory depression ($P < 0.01$) than with methohexitone. Initial clinical recovery was more rapid after propofol ($P < 0.01$) and at 20 min patients were more alert ($P < 0.01$) with better choice reaction times ($P < 0.05$) than the methohexitone group. Ataxia was common in both groups at 20 min, but by 40 min there was a significant improvement in the propofol patients ($P < 0.01$). There was no significant difference in postoperative sequelae between the groups. Despite greater cardiovascular and respiratory depression, propofol may well be the induction agent of choice for day-case anaesthesia.

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PREMEDICATION: EFFECT ON INDUCTION OF ANAESTHESIA WITH PROPOFOL

J. S. C. McCOLLUM*, J. W. DUNDEE AND
R. J. T. CARLISLE*
Department of Anaesthetics, The Queen's University of Belfast

Propofol has been reformulated as an emulsion following adverse reactions with the Cremophor EL preparation. It induces anaesthesia rapidly and smoothly although dose- and age-related arterial hypotension and respiratory depression occur.

Opioid premedication made induction reliable with 1.5 mg kg^{-1} of the original formulation (Briggs et al., 1982), but in a more recent study Briggs and White (1985) found that it affected neither the incidence of side effects nor the degree of cardiorespiratory depression.

We report here the influence of four commonly used premedicants on propofol induction. The study, for which Regional Medical Ethical Committee approval had been obtained, was carried out on 320 fit subjects of either sex for whom i.v. induction of anaesthesia was indicated. They were randomly allocated to receive either no premedication or diazepam 10 mg orally, pethidine 50 mg + atropine 0.6 mg i.m., papaveretum 15–20 mg + hyoscine 0.3–0.4 mg i.m. 60–120 min before operation. Anaesthesia was induced with propofol 1.75, 2.0, 2.25 or 2.5 mg kg^{-1} given over 20 s, subsequent observations comprising success of induction, cardiorespiratory depression, pain on injection and incidence of excitatory or respiratory upset.

Statistical analysis was with Chi-square or Fisher's exact probability testing where appropriate.

Induction with 1.75 mg kg^{-1} was most successful following premedication with papaveretum–hyoscine (table XI). Premedication did not affect systolic arterial pressure decrease at 2 min, which varied between 9 and 16%. Respiratory depression was not markedly potentiated by opiate premedication, with apnoea exceeding 60 s occurring in all groups receiving 2.5 mg kg^{-1}. Premedication did not affect the incidence of excitatory or respiratory side effects.

TABLE XI. *Percentage of patients induced following each premedicant and dose of propofol* (n = *20*). *P < *0.01 compared with unpremedicated group*

	Propofol (mg kg^{-1})			
Premedication	1.75	2.0	2.25	2.5
Nil	65	85	95	100
Diazepam	85	100	90	100
Pethidine–atropine	85	100	95	100
Papaveretum–hyoscine	100*	100	100	100

Pain on injection following dorsum of hand injection was reduced ($P = 0.08$) by opiate premedication from 34% to 20%. Diazepam premedication did not affect this incidence.

Propofol is compatible with commonly used premedicants, with induction requirements in adults reduced by papaveretum + hyoscine to 1.75 mg kg^{-1}.

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PLASMA BUPIVACAINE CONCENTRATIONS ASSOCIATED WITH EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION: INFLUENCE OF PRETREATMENT WITH RANITIDINE

C. M. WILSON*, J. MOORE, R. G. GHALY*,
E. McCLEAN* AND J. W. DUNDEE
Department of Anaesthesia, The Queen's University of Belfast

H_2-receptor antagonists, which are increasingly being used in obstetrics, have many actions and could conceivably affect metabolism of local anaesthetics. We report a study of plasma bupivacaine concentration in 16 patients having an elective Caesarean section under extradural anaesthesia using the incremental method described by Thompson and colleagues (1985). Nine received ranitidine 150 mg by mouth 2 h before the procedure.

Venous blood was withdrawn before and at 10-min intervals for 1 h after starting the block and at delivery, when umbilical vein blood was also sampled. It was analysed for bupivacaine by HPLC, with u.v. detection at 220 nm.

Patient characteristics were similar in both groups, as was the mean dose of bupivacaine and mean time taken to achieve the desired block (table XII).

TABLE XII. *Bupivacaine and block data (mean ± SEM)*

n	Ranitidine	Total dose (mg)	Time to max. block (min)
7	–	114±7.1	46±3.5
9	+	124±8.5	54±2.8

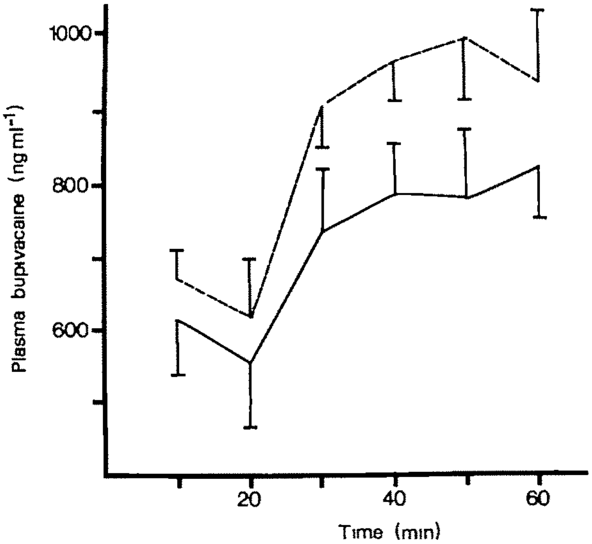

FIG. 1. Plasma bupivacaine concentrations (mean ± SEM) during extradural anaesthesia for Caesarean section over the period of study. —— Ranitidine pretreatment; —— no ranitidine.

Patients pretreated with ranitidine had higher mean plasma bupivacaine concentrations than those receiving no therapy (fig. 1), the difference becoming significant at 40 min ($P < 0.05$).

There was no significant difference between the mean maternal (MV) or umbilical vein (UV) plasma bupivacaine concentrations or the respective UV:MV drug ratios, at delivery in the two groups.

The venous plasma bupivacaine concentrations remained less than the toxicity range in both series. However, the influence of ranitidine on bupivacaine plasma concentrations, as shown here, is an important finding and worthy of further study.

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ACUPUNCTURE REDUCED THE EMETIC EFFECTS OF NALBUPHINE PREMEDICATION

A. G. A. LYNAS*, R. G. GHALY*, AND J. W. DUNDEE
Department of Anaesthetics, The Queen's University of Belfast

Chestnutt and Dundee (1985) have demonstrated the ability of acupuncture (ACP) at the P6 site (Lynas et al., 1986) to reduce the emetic sequelae in women premedicated with meptazinol 100 mg undergoing a standard operation under standard anaesthesia, as compared with a group given meptazinol alone. This study had only control (no therapy) and acupuncture (P6) groups and there was a possible element of bias in selection of patients who agreed to acupuncture; there may also have been some psychological effect from "needling".

We report findings of a comparable study in three groups of 25 women, including a series in which a "dummy" (lateral crease right elbow) ACP point was stimulated, but using nalbuphine 10 mg as premedication. This was a randomized single-blind study, the emetic observations being made by a person who did not perform the acupuncture. Patients in all groups were broadly comparable with respect to age, weight and duration of anaesthesia. Verval consent was obtained and the study was approved by the local Medical Research Ethical Committee.

TABLE XIII. *Incidence of vomiting (with or without nausea) (V) and nausea alone (N), in three comparable groups each of 25 patients premedicated with nalbuphine 10 mg. Patients received either the premedication alone or ACP at P6 point (active) or right elbow (dummy point)*

	No ACP		Acupuncture			
			Active point		Dummy point	
	V	N	V	N	V	N
Preoperative	1	7	0	3	2	6
Postoperative						
0–1 h	3	12	0	3	3	7
1–6 h	3	12	0	3	2	9
0–6 h	6	11	3	3	5	12
Total periop.	7	11	3	3	6	13

P6 ACP significantly reduced ($P < 0.02$–0.001) postoperative emetic sequelae as compared with no adjuvant therapy (table XIII). Late and overall postoperative and total perioperative sequelae were significantly less ($P < 0.05$–0.001) in patients given P6 compared with dummy ACP. There was no significant difference in the incidence of emetic sequelae in patients having dummy ACP and those having no adjuvant therapy.

Considering patients with no active vomiting, 11/19 in the control group and 12/20 in the dummy ACP group were nauseated, compared with only 3/22 in those having P6 ACP;

the efficacy of the latter in reducing nausea was significant ($0.05 > P > 0.02$).

Since perioperative ambulation, which is an important factor influencing nausea and vomiting, was constant in all three groups, this study shows a definite protective role of P6 acupuncture against nalbuphine-induced emetic effects. Even though the needling was only for 5 min immediately after drug administration, its protective effect lasted for at least 6 h.

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EFFECTS OF AGE AND CARDIAC SHUNTS ON THE RATE OF UPTAKE OF NITROUS OXIDE IN CHILDREN

A. C. O'CALLAGHAN*, G. KOREN* AND I. A. J. SLOAN*

Department of Anaesthesia and Division of Clinical Pharmacology, The Hospital for Sick Children and University of Toronto

The concept of clearance fraction of anaesthetic agents was applied to the uptake and excretion of inhalation agents by Severinghaus (1963). We applied a pharmacokinetic equation, previously described for renal clearance (Gibaldi and Perrier, 1982), to the uptake of nitrous oxide (N_2O) in order to calculate the elimination half-life ($T_{\frac{1}{2}}$) of N_2O when administered at a constant rate and eliminated unchanged through the lungs. Elimination $T_{\frac{1}{2}}$ from the alveoli is inversely related to rate of uptake of N_2O by the lungs. By using this principle, we have compared the rate of uptake of N_2O in different study groups.

The rate of uptake of N_2O was measured in 33 normal children undergoing non-cardiac surgery, 17 children with right (R)–left (L) shunts and 18 children with L–R shunts. Eight of the 18 children with L–R shunts underwent cardiac catheterization before operation.

In all children anaesthesia was induced with sodium thiopentone 5–6 mg kg^{-1}, atropine 0.02 mg kg^{-1} and suxamethonium 1.5–2 mg kg^{-1}. The children were manually ventilated with 100% oxygen and intubated. Patients were then ventilated with a Sechrist ventilator preset to deliver 70% nitrous oxide in oxygen, at a frequency of 20 b.p.m., inspiratory:expiratory ratio of 1:2 and minute volume calculated to produce normacapnia.

Gases were sampled continuously at 200 ml min^{-1} through a fine-bore nylon tube connected to a Teflon catheter, the tip of which was positioned 0.5–1 cm from the distal end of the tracheal tube. N_2O concentration was continuously measured by a Beckman LB2 infrared gas analyser and recorded using a Hewlett-Packard 7004B chart recorder.

End-tidal inspired and end-tidal expired N_2O concentrations were measured and the fractional expired N_2O concentration for each breath was calculated. The cumulative fractional expired N_2O concentration was plotted against time. The plot is curvilinear initially, but soon becomes linear. Extrapolation of the linear segment from the 90% steady state position yields an intercept with the time axis = $T_{\frac{1}{2}}/0.693$.

Statistically significant differences ($P \leqslant 0.05$) in elimination $T_{\frac{1}{2}}$ among the three groups were determined using analysis of variance. The correlations of elimination $T_{\frac{1}{2}}$ with age were tested by least squares linear regression analysis.

Elimination $T_{\frac{1}{2}}$ increased with age in all three groups. An R–L shunt did not affect the rate of uptake compared with normal children, whereas an L–R shunt decreased the rate of uptake in children younger than 3.5 yr and increased the rate of uptake in children older than 3.5 yr. Elimination $T_{\frac{1}{2}}$ in children with L–R shunts increased with the shunt fraction.

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COMPARISON OF THE ANALGESIC AND SEDATIVE EFFECTS OF NALBUPHINE AND MORPHINE FOLLOWING HIP REPLACEMENT

M. M. BRADY*, G. FURNESS AND J. P. H. FEE

Department of Anaesthesia, The Queen's University of Belfast

Nalbuphine is a partial opioid agonist/antagonist with a depressant effect on respiration similar to equivalent doses of morphine (Gal, Difazio and Moscicki, 1982). The most commonly occurring side effects are sedation and drowsiness. It is superior to morphine in relieving the pain of myocardial infarction and reducing myocardial oxygen demand (Lee et al., 1981). We have compared the analgesic and sedative effects of equivalent doses of nalbuphine and morphine in patients undergoing total hip replacement.

The study, to which patients gave informed consent on the night before operation, was approved by the local Medical Ethical Research Committee. Two groups of 40 patients received either nalbuphine 0.3 mg kg^{-1} or morphine 0.15 mg kg^{-1} in random order perioperatively. Ages ranged from 15 to 75 yr: all conformed to ASA physical status I or II. None was receiving any opioid or sedative medication. Sixty minutes before operation, each was premedicated with 0.03 ml kg^{-1} of the coded drug i.m. A standard anaesthetic of thiopentone, nitrous oxide, oxygen and isoflurane was used.

Immediately after operation, the analgesic effect was assessed by a trained observer. The opioid was administered

TABLE XIV. *Pain intensity at the times shown after nalbuphine (40 patients; 22 male) or morphine (40 patients; 12 male) postoperative analgesia*

	Nalbuphine				Morphine			
	Time (min)				Time (min)			
	0	60	120	180	0	60	120	180
Pain								
Severe	34	16	15	14	32	5	4	5
Moderate	0	14	12	14	0	24	15	15
Nil	0	4	7	6	0	3	13	12
No postoperative analgesia needed	6				8			

on request from the patient and, if needed, repeated after a minimum of 3 h. Pain intensity, relief and sedation were noted on recovery and following injection at 30-min intervals for 2 h and hourly for 6 h. Pain intensity was graded by the patient as severe, moderate or none. Relief was assessed by the observer as slight, moderate or complete. Sedation was assessed at the same time on a four-point scale.

Initial pain severity in patients requiring postoperative analgesia was similar in both groups (table XIV). Ten patients who received nalbuphine and two who received morphine had inadequate analgesia and required additional i.v. opioid. The incidence differed significantly ($P < 0.05$) with the two drugs. For the purpose of analysis, these 12 were graded as having severe pain during the first 3 h of the study. Morphine produced the better analgesia at 60, 120 and 180 min ($P < 0.05$–0.01, Mann–Whitney U test). There was no difference in the degree of sedation with either drug.

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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION: COMPARISON OF NALMEFENE WITH NALOXONE

K. M. KONIECZKO*, M. P. BARROWCLIFFE,
C. JORDAN* J. G. JONES
Division of Anaesthesia, Clinical Research Centre, Harrow

Nalmefene is a new opiate antagonist with a β elimination half-life of 8 h and a claimed potency two to five times that of naloxone. This study was designed to compare the potency and duration of action of nalmefene, high and low dose naloxone and saline placebo. The model used was morphine-induced respiratory depression.

Six healthy male volunteers received morphine 10 mg/70 kg i.m. followed 1 h later by one of the test drugs i.v.: nalmefene 0.4 mg/70 kg, naloxone 1.6 mg/70 kg, naloxone 0.4 mg/70 kg or saline placebo. Each subject was studied on four occasions, and the test drugs were administered double-blind in a random sequence.

Baseline values were obtained before administration of morphine. The measured respiratory variables were end-tidal P_{CO_2} ($P_{E'CO_2}$) and respiratory rate (RR) averaged over 7 min, followed by the ventilatory response to hypercapnia, using a modified Read rebreathing technique. Repeated measures were made over a 7-h period.

The mean value for the six subjects of resting $P_{E'CO_2}$, RR, log slope of the ventilatory response to hypercapnia and log of ventilation at $P_{E'CO_2}$ 8 kPa (log $\dot{V}_{E}8$) were calculated for each treatment.

Data were divided into three time periods; (1) first 1.5 h after treatment, (2) subsequent 2 h and (3) the final 2.5 h. The changes from baseline were compared using a two-way analysis of variance for each separate period. There were significant differences between the four treatments in $P_{E'CO_2}$, log slope and log $\dot{V}_{E}8$. Paired t testing using the residual standard deviations showed the difference between nalmefene and naloxone increased over time. In the second and third periods, nalmefene was significantly different from naloxone 0.4 mg and in the third time period it was significantly different from nalaxone 1.6 mg.

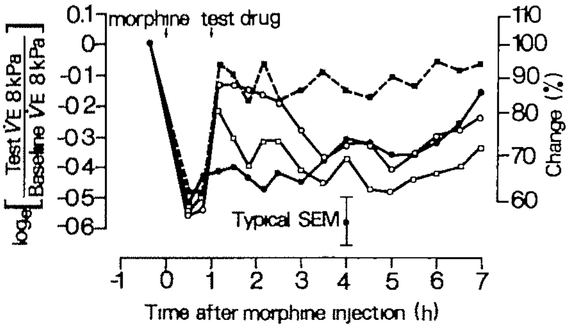

FIG. 2. Change in log $\dot{V}_{E}8$ from baseline. ■ = Nalmefene 0.4 mg/70 kg; ● = placebo; □ = naloxone 0.4 mg/70 kg; ○ = naloxone 1.6 mg/70 kg.

The results (fig. 2) demonstrate that this dose of nalmefene has a longer duration of action than four times the conventional dose of naloxone.

FAILURE OF AMINOPHYLLINE OR DOXAPRAM TO ANTAGONIZE MIDAZOLAM-INDUCED SEDATION

H. M. L. MATHEWS*, R. J. T. CARLISLE* AND
J. P. H. FEE
Department of Anaesthetics, The Queen's University of Belfast

I.v. aminophylline has been used to antagonize postoperative sedation from diazepam (Stirt, 1981; Arvidsson et al., 1984). Doxapram has also been shown to be effective in antagonizing diazepam-induced sedation (Allen and Gough, 1983) Midazolam is a useful i.v. sedative and anaesthetic induction agent. The aim of this study was to evaluate the effects of aminophylline or doxapram on midazolam sedation.

Thirty fit, unpremedicated patients aged 18–60 yr undergoing arthroscopy of the knee joint were included in the study. Average operating time was 24.2 min. Anaesthesia was induced with midazolam 0.3 mg kg^{-1} injected i.v. over 20 s and maintained with nitrous oxide in oxygen and isoflurane. In the recovery ward 60 min after the midazolam injection, the degree of sedation was assessed on a four-point scale ranging from deeply asleep (4) to fully alert (1). The patients were then randomly allocated in a double-blind fashion to receive aminophylline 2 mg kg^{-1}, doxapram 1 mg kg^{-1} or an equivalent volume of saline i.v. over 3 min. The degree of sedation was reassessed at 15-min intervals until 1 h after the injection.

A further 10 patients received either aminophylline 2 mg kg^{-1} or saline i.v. 60 min after the original midazolam injection. Blood samples were taken before the midazolam injection and at 40, 50, 60, 70, 80 and 90 min following the midazolam. Total plasma midazolam concentrations were estimated using gas–liquid chromatography (Howard, McLean and Dundee, 1985).

Patients were broadly comparable with relation to age, weight and fitness. The distribution of sedation scores was similar in all three groups at all times of observation and no statistical difference was found between groups using the

Mann–Whitney *U* Test. With one exception (saline group), all patients were awake at 120 min after administration of midazolam.

TABLE XV. *Mean ± SEM plasma midazolam concentration* ($ng\ ml^{-1}$). *Aminophylline or saline injected after 60 min sample*

Time (min)	Aminophylline	Saline
40	160 ± 6.6	193 ± 15.1
50	148 ± 10.3	174 ± 17.1
60	162 ± 30.8	176 ± 8.7
70	135 ± 11.7	167 ± 12.3
80	132 ± 17.2	147 ± 10.1
90	120 ± 13.5	132 ± 18.4

Neither doxapram nor aminophylline is an effective antagonist to midazolam.

Table XV shows that aminophylline had no effect on the rate of decay of plasma midazolam concentrations.

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PROTECTION OF REGIONAL FUNCTION OF ISCHAEMIC MYOCARDIUM BY BETA-BLOCKADE

B. LEONE, J. J. LEHOT, C. M. FRANCIS,
G. R. CUTFIELD, P. FOËX AND W. A. RYDER
Nuffield Department of Anaesthetics, University of Oxford

Protection of left ventricular performance by beta-blockade during myocardial infarction has been demonstrated (Libby et al., 1973). The present study was undertaken to observe the effects of beta-blockade on compromised myocardium.

Six dogs were premedicated with morphine, anaesthetized with halothane in 30% oxygen and 70% nitrogen and ventilated to maintain normocarbia. Each dog was instrumented to measure aortic pressure, aortic flow, blood flow in the left anterior descending coronary artery, left ventricular pressure and its first derivative (LV dP/dt). Sonomicrometry was used to measure wall motion in the territories of the left anterior descending (LAD) and left circumflex (LC) coronary arteries. A micrometer-controlled snare was placed around the LAD. A halothane dose–response curve up to 2.0% was performed in each of the three phases: control, critical constriction and critical constriction 30 min after the administration of oxprenolol 0.3 mg kg^{-1}. Critical constriction was defined as the degree of narrowing sufficient to abolish the hyperaemic response following a 10-s total occlusion of the LAD.

After critical constriction, high halothane caused substantial and significantly greater post-systolic shortening (PSS) (Lowenstein et al., 1981) in the LAD segment compared with the small amount of PSS seen before critical constriction (table XVI). Administration of oxprenolol while critical constriction was present resulted in significantly less PSS than with critical constriction alone. No significant effects on left ventricular performance were noted, as reflected in LV dP/dt_{max}.

TABLE XVI. *Data (mean (SEM)) at 2.0% halothane for % PSS and LV* dP/dt. *$P < 0.05$ v. *control and* v. *critical constriction with oxprenolol (two-way analysis of variance)*

	% PSS	LV$dP/dt_{max}$ (mm Hg)
Control	11 (6)	550 (76)
Critical constriction	29 (9)*	483 (83)
Crit. constr. + Oxprenolol	10 (7)	575 (85)

This study shows that oxprenolol administration can reverse regional dysfunction seen with critical constriction under halothane anaesthesia, decreasing PSS to a value seen with normal coronary circulation. The protection of myocardial function has been attributed to the negative inotropic effects of beta-blockers (Libby et al., 1973). However, no such effcts were observed in this preparation. Therefore, beta-blockers may protect the myocardium during ischaemia by improving myocardial oxygen utilization and metabolism, rather than by decreasing global myocardial oxygen demand.

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ENDOCARDIAL VIABILITY RATIO (EVR) AND ISCHAEMIC DYSFUNCTION OF THE LEFT VENTRICLE

J. J. LEHOT, B. LEONE, C. M. FRANCIS,
G. R. CUTFIELD, AND **P. FOËX**
Nuffield Department of Anaesthetics, University of Oxford

EVR has been proposed as a reliable index of oxygen supply: demand ratio of the normal myocardium (Hoffman and Buckberg, 1978). This index is used in patients with coronary artery disease (Massaut et al., 1983), but there has been no study relating EVR with regional ischaemia.

In 13 dogs premedicated with morphine 0.3 mg kg^{-1}, intubated and ventilated to maintain normocarbia, the responses to increasing concentrations of halothane (up to 2%) in oxygen were recorded before and after critical constriction of the left anterior descending coronary artery (LAD). Aortic and left ventricular pressures and aortic blood flow were measured. Regional wall motion was measured with ultrasonic length detectors implanted at the subendocardium in territory supplied by LAD and left circumflex coronary artery (LC).

EVR was calculated as the ratio of the diastolic pressure time index (DPTI) and systolic pressure time index (SPTI), measured by planimetry of high fidelity hard copy recordings.

Dose-dependent depression of global and regional function (systolic shortening) was observed in response to halothane. Before LAD constriction, 2% halothane reduced systolic shortening to a smaller fraction of control in LAD (61 ± 4% (mean ± SEM)) than in LC segment (72 ± 6%). This difference was significant ($P < 0.01$, analysis of variance, Duncan's test). After critical constriction of the LAD, halothane caused more depression of this segment than before constriction ($47 \pm 6\%$ *v.* $61 \pm 4\%$) ($P < 0.01$), while function of the LC segment was less depressed ($90 \pm 8\%$ *v.* $72 \pm 6\%$) ($P < 0.01$). With critical constriction, post-systolic shortening (PSS) (0.6 ± 0.15 mm) developed in the LAD segment ($P < 0.01$, *v.* control). EVR decreased from 1.38 ± 0.08 to 1.15 ± 0.04 ($P < 0.01$) with increasing halothane concentration before critical constriction and from 1.30 ± 0.07 to 1.06 ± 0.04 ($P < 0.01$) after critical constriction. However, there was a linear correlation between increase in PSS and reduction in EVR ($r = 0.65$; $P < 0.025$). Moreover, there was little PSS (0.08 ± 0.04 mm) when EVR was greater than 1.25, and substantial PSS (0.66 ± 0.18 mm) when EVR was less than 1.0 ($P < 0.01$). Similarly, EVR was higher when PSS was absent (1.21 ± 0.04) than when it was present (1.08 ± 0.04) ($P < 0.025$).

This study shows that, in a model of critical constriction of a major coronary artery and under halothane anaesthesia, reductions in EVR are associated with ischaemic dysfunction. It also shows that the function of a normal segment may be enhanced when ischaemic dysfunction of a compromised segment is present.

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INFLUENCE OF CARDIAC DRUGS ON THE CARDIOVASCULAR EFFECTS OF ATROPINE AND GLYCOPYRROLATE

W. P. BLUNNIE*, E. J. BOURKE* AND
L. P. CLAFFEY*
Department of Anaesthesia, Mater Misericordiae Hospital, Dublin

It is common practice in anaesthesia to antagonize residual non-depolarizing neuromuscular blockade at the conclusion of surgery with a mixture of neostigmine and an anticholinergic agent.

Since the advent of intrathecal morphine, early extubation following open heart surgery has become feasible (Mathews and Abrams, 1980). In the intensive care unit, ventilation is continued with 50% nitrous oxide with oxygen until the core temperature is 37 °C and skin temperature 30 °C. The nitrous oxide is discontinued and the patient is allowed to wake. The antagonist mixture of either atropine or glycopyrrolate with neostigmine is administered.

In this study we compared changes in heart rate and rhythm, arterial pressure, rate–pressure product and secretions after the administration of neostigmine and atropine with those obtained with neostigmine and glycopyrrolate after coronary artery bypass grafting. Seventy-six patients were studied (34 in the atropine group and 42 in the glycopyrrolate group). The drugs were administered on a double-blind basis in a preset dose regimen. Patients on inotropic support, anti-arrhythmic, anticholinergic, pre- or after-load reduction drugs during operation were excluded—as were those requiring such medication during the period of study.

The groups were similar with respect to age, weight and preoperative medication.

In the glycopyrrolate group there was a gradual increase in heart rate for all drugs over 7 min, returning to base line in 25 min. Rate–pressure product was increased by 18%. Overall, glycopyrrolate had advantages over atropine except in patients receiving beta-blockers, in whom the increase in heart rate and rate–pressure product were higher.

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CONDITIONS AND CRITERIA FOR CREAMING OF INTRALIPID

S. G. RADFORD*, G. BIDDULPH* AND
A. M. S. BLACK
Sir Humphry Davy Department of Anaesthesia, University of Bristol

Intralipid is used as a vehicle for some water insoluble anaesthetic agents. The lipid emulsion is agglutinated or "creamed" when mixed *in vitro* with serum from acutely ill patients. The *in vitro* creaming tendency increases with increasing concentrations of C-reactive protein (Hulman et al., 1982). *In vivo* creaming may alter the availability of drugs carried by Intralipid, and may have more directly adverse effects when Intralipid is used for i.v. feeding. However, the *in vivo* relevance of *in vitro* creaming tests is not clear. The conditions of the test, and the criteria by which the results are judged are arbitrary.

We tested the sera of 20 patients before, and 48 h after, uncomplicated major abdominal surgery, to estimate the incidence of *in vitro* creaming under two different conditions of testing, and with two different criteria for judging the results. We incubated 400 µl of the patient's serum for 24 h at 37 °C with 10 µl of either 2% or 20% Intralipid, and judged the results either macroscopically or microscopically. Under the microscope, we defined four grades of creaming, based on the relative amount of unagglutinated and agglutinated Intralipid—grade zero indicating no agglutination, and grade 3 indicating complete agglutination.

If patients in grades 1, 2 and 3 were all designated "creamers", the incidence of creaming was 75% with the 2% Intralipid and 90% with the 20% Intralapid. If creamers were designated only on the basis of macroscopic creaming, the incidence was 50% with either concentration.

In each of 15 further patients, we took between five and nine serial blood samples, starting before operation, and continuing for 48 h after operation. *In vitro* creaming tests were carried out with both concentrations of Intralipid, and the creaming grades were determined by a single microscopist (S.R.), from whom the sampling order was concealed. We also measured the concentrations of some acute phase proteins. Most of these increased steadily, after a latent period, to a maximal recorded value at 48 h. Creaming grades tended to be lower with the 2% than with the 20% Intralipid, but the two tests agreed to within one grade in 96% of cases. The grades by either test were higher at 48 h than before operation, but the increase was not a steady, unidirectional progression. Thus, for C-reactive protein, there was rarely a convincing relationship, in individual patients, between increasing C-reactive protein concentration and increasing creaming grade. We suspect that this was because of the limited precision of the microscopic grading, even when done with all reasonable care. When results from all 15 patients were pooled, the relationship did appear, as did a similar relationship between increasing creaming grade and increasing concentration of alpha-1-antitrypsin.

Our interpretation is that an *in vivo* change in the reaction to Intralipid did occur, and that it coincided with the acute phase protein response, but that the tests for detecting the change are somewhat arbitrary and are too imprecise to be useful in individual cases.

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RESPIRATORY HYDROCARBONS

P. M. PFEIFER*, AND C. J. HULL
Department of Anaesthesia, University of Newcastle upon Tyne

A method has been developed for the measurement of trace concentrations of hydrocarbons in expired air. The method includes a 500-fold concentration step and is sufficiently sensitive to detect background concentrations in room air.

Ten litre of expired breath is aspirated at a defined flow rate through a 12-cm Porasil C column at −78 °C. The trapped hydrocarbons are released into a 20-ml glass syringe by immersion of the column in boiling water. Five-millilitre aliquots of this concentated gas sample are injected onto a 3-m Porasil C gas–liquid chromatography (GLC) column fitted with a flame ionization detector.

The upper GLC trace on figure 3 shows the hydrocarbons present in room air. The peaks labelled a, c and d are n-butane, n-pentane and n-hexane respectively; peak b is iso-pentane. Using gas mixtures containing known concentrations of n-pentane, the linearity of the flame ionization detector response was demonstrated. The reproducibility of the cold column concentration process was shown to be in the region of ±20%.

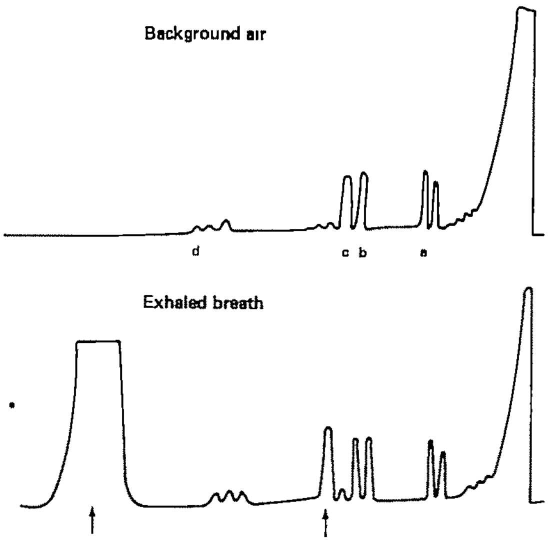

FIG 3. GLC trace from concentrated expired gas.

Calibration of the detector response to n-pentane shows that it can be detected at concentrations of 0.1 ng litre^{-1}. Typical n-pentane concentrations in the expired breath of normal volunteers breathing room air are in the region of 1 ng litre^{-1}.

Figure 3 also demonstrates the two major endogenous hydrocarbons produced (arrows) by normal unanaesthetized subjects. The largest peak is isoprene, precursor of cholesterol, the other is as yet unidentified.

The method is currently applied to the measurement of expired n-pentane, which may be regarded as a marker of lipid peroxidation induced by toxic metabolites of oxygen. The metabolism of the volatile anaesthetic agents is also being studied. The GLC trace of exhaled breath from anaesthetized patients exposed to halothane contains two additional peaks which are not present in halothane itself. Factors that affect halothane metabolism may be of clinical interest, especially those that promote reductive metabolism, which has been postulated to be the cause of halothane hepatitis.

MALIGNANT HYPERPYREXIA: A RETROSPECTIVE ANALYSIS EXAMINING MEDICAL, PERSONAL AND FAMILY HISTORY

R. J. SMITH*, H. F. NEWBEGIN*, F. R. ELLIS AND G. M. MILLS*
Department of Psychiatry and Anaesthesia, University of Leeds, and School of Psychology, University of Bradford

Malignant hyperpyrexia (MH) was first described in 1960 by Denborough and Lovell, and since has been claimed to be the single largest cause of anaesthetic mortality in apparently fit young adults. At present, no single non-invasive test for MH has been discovered, and definitive diagnosis requires a muscle biopsy. Identification before anaesthesia would therefore have a major influence on mortality rate. Consequently, this study attempted to produce a predictive screening test of MH susceptibility, using a questionnaire survey of known MH probands and anaesthetic controls.

A novel questionnaire covering 45 questions on medical, personal and family history was sent to 279 patients who were biopsied in Leeds for suspected MH. Of these 160 were MH-positive, and the remaining 119 were MH-negative. A further 196 questionnaires were sent to a control group of patients who had received an equivalent operation/anaesthetic but who had had no reported anaesthetic reaction. The control group were matched to the MH-positive group for age and sex.

Ninety-six MH-positive patients, 79 MH-negative patients, and 168 control patients returned the questionnaire. Discriminant function analysis using all variables proved capable of discriminating significantly between the three groups of patients with a classification accuracy of 71%.

Whilst the questionnaire cannot yet replace the present definitive diagnosis by muscle biopsy, our results provide the foundation for future research for an alternative, non-invasive screening method. This research is presently in progress, using a computerized questionnaire.

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SELECTIVE TOLERANCE OF GROUP III AND IV SOMATOSYMPATHETIC REFLEXES TO THE EFFECTS OF ALFENTANIL

G. ODENSJO SWENZEN*, M. K. CHAKRABARTI, S. SAPSED-BYRNE* AND **J. G. WHITWAM**
Anaesthetics Department, Royal Postgraduate Medical School, London

Schmidt and Livingston (1933) and Askitopoulou and colleagues (1985) have shown the development of acute tolerance within 3 h to the antinociceptive effects on the circulation of morphine and fentanyl, respectively. This study investigated the possibility of selective tolerance of group III ($A\delta$) and IV (C) somatosympathetic reflexes to the effects of alfentanil.

Six dogs were anaesthetized with chloralose and paralysed with suxamethonium, and the lungs artifically ventilated to normal Pa_{CO_2}. Supramaximal electrical stimuli were applied to the radial nerve. Evoked responses were recorded in renal sympathetic nerves exposed retroperitoneally close to the renal artery. An infusion of alfentanil 20 $\mu g\ kg^{-1}\ min^{-1}$ was administered until the group IV response was just abolished and then increased to 200 $\mu g\ kg^{-1}\ min^{-1}$ until the group III evoked sympathetic response was also abolished. The preparations then recovered until the evoked responses were approximately 50% of the control values. Incremental doses of alfentanil (7.5, 12, 19, 30, 45, 75 and 120 $\mu g\ kg^{-1}$) were then administered at intervals of 10 min, followed by a bolus dose of alfentanil 500 $\mu g\ kg^{-1}$. The preparation was then tested with further bolus doses of between 1500 and 2000 $\mu g\ kg^{-1}$.

During the initial infusion of alfentanil, the late group IV and early group III responses were abolished by mean doses of 68 $\mu g\ kg^{-1}$ (SEM 3.2 $\mu g\ kg^{-1}$) and 797 $\mu g\ kg^{-1}$ (SEM 120 $\mu g\ kg^{-1}$), respectively. After subsequent conditioning with alfentanil in two preparations, both the group IV and group III responses became tolerant to the effects of large bolus doses of the drug. In the other four preparations the group IV response was still eliminated by the drug, but the group III response showed selective tolerance. The mean heart rate and arterial pressure were reduced by 45% and 29%, respectively, during the initial infusion of alfentanil. Naloxone restored the sympathetic responses, heart rate and arterial pressure to control values.

The maximal effect on the resting circulation occurred at a dose of alfentanil which just eliminated somatosympathetic reflexes evoked by C fibres. Selective tolerance of the $A\delta$ reflex implies that the drug would fail to abolish major nociceptive cardiovascular responses mediated by $A\delta$ fibres, even though it was still capable of causing "analgesia" by abolition of the effects of C fibres, which in man appear to be the principal component in perceived pain (Collins et al., 1960).

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CONTINUOUS MONITORING OF PLASMA POTASSIUM DURING INFUSIONS OF DOPAMINE, DOBUTAMINE AND ISOPRENALINE IN DOGS

H. F. DRAKE* AND T. TREASURE*
Department of Medicine & Cardiac Surgery Unit, The Middlesex Hospital, London

Adrenergic agonists including adrenaline, salbutamol and isoprenaline, cause hypokalaemia in animals (Todd and Vick, 1971) and in man (Vincent et al., 1984), by beta$_2$-receptor stimulated uptake of potassium into skeletal muscle and the liver. Dopamine and dobutamine—principally beta$_1$-stimulants, but with some beta$_2$-activity—have not been closely examined for this effect. Infusions of these drugs were compared with isoprenaline by catheter-tip ion-selective electrode recording of arterial potassium.

Sixteen adult beagles were anaesthetized with thiopentone and pentobarbitone. Potassium electrodes similar to those previously described (Linton, Lim and Band 1982) were placed in the aorta via the femoral artery. Dopamine and dobutamine 10 and 30 $\mu g\ kg^{-1}\ min^{-1}$ and isoprenaline 0.07 and 0.2 $\mu g\ kg^{-1}\ min^{-1}$ were studied. The drugs were infused in random order for 30 min, preceded and followed by a similar period of saline infusion. Each dog received three, four or five drug treatments. The potassium concentration was read from the tracing from the indwelling electrode.

The results are summarized in table XVII. A consistent pattern was seen, of a small initial increase in potassium (except in 2/10 dogs in the low dose dopamine group), followed by a sustained decrease (all animals).

Thus, dopamine, dobutamine and isoprenaline all caused significant changes in arterial potassium in dogs.

TABLE XVII. *Potassium (mmol litre^{-1}) (mean ± SEM) from an aortic electrode during infusions of inotropic drugs. Dp10, Dp30 = dopamine 10 and 30 $\mu g\ kg^{-1}\ min^{-1}$; Db10, Db30 = dobutamine 10 and 30 $\mu g\ kg^{-1}\ min^{-1}$; I0.07, I0.2 = isoprenaline 0.07 and 0.2 $\mu g\ kg^{-1}\ min^{-1}$. C, Mx, Mn, 15 and 25 show potassium control, peak, trough and at 15 and 25 min of infusion* (n = *10 in each group). Significant changes from control:* *P < *0.005*, **P < *0.01* (*Wilcoxon's test for paired differences*)

	Dp10	Dp30	Db10	Db30	I0.07	I0.2
C	3.4±0.2	3.3±0.2	3.1±0.2	3.5±0.2	3.4±0.2	3.4±0.2
Mx	3.5±0.2 ns	3.6±0.2**	3.3±0.2**	3.9±0.2**	3.5±0.2**	3.6±0.2**
Mn	2.6±0.1**	2.5±0.1**	2.4±0.1**	2.5±0.1**	2.6±0.1**	2.1±0.1**
15	2.8±0.1*	2.5±0.1**	2.5±0.1**	2.6±0.1**	2.7±0.1**	2.4±0.1**
25	2.6±0.1**	2.5±0.1**	2.5±0.1**	2.5±0.1**	2.6±0.1**	2.2±0.1**

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INDUCTION CHARACTERISTICS OF PROPOFOL COMPARED WITH OTHER I.V. ANAESTHETICS

J. S. C. McCOLLUM*, J. W. DUNDEE*.
F. P. ROBINSON* AND H. M. L. MATHEWS*
Department of Anaesthetics, The Queen's University of Belfast

COMPARISON OF ORAL MIDAZOLAM AND TEMAZEPAM WITH PLACEBO AS PREMEDICATION FOR DAY CASE PATIENTS

J. HARGREAVES*
Department of Anaesthesia, University Hospital of South Manchester

A controlled comparison of midazolam 15 mg and temazepam 20 mg as premedication in 90 short-stay patients undergoing minor surgery was carried out. Midazolam, with a shorter elimination half-life than temazepam, may be preferable for this purpose.

Patients presenting for day-case surgery were given the option of an oral premedication. Those who accepted were included in the trial. The 30 patients in each group received oral premedication which was randomized and double-blind, approximately 1 h before operation. Before premedication and induction of anaesthesia, anxiety was measured (LAS), together with subjective and objective assessments of sedation and quality of premedication. The dose of thiopentone and concentration of inhalation agent required for anaesthesia were noted. Arterial pressure, heart rate and oral temperature were measured on admission, before induction and at 1 h and 3 h after operation. Tests of recovery comprised: time to waking, ability to walk unaided at 3 h, digit–symbol substitution and eye divergence measured by Maddox Wing; the last two tests were carried out at 1 h and 3 h after anaesthesia and compared with readings obtained before medication. Side effects were noted and memory for simple anaesthetic-related events recorded.

Midazolam and temazepam were both found to be superior to placebo regarding preoperative anxiolysis and sedation (midazolam > temazepam > placebo). Patients who received midazolam required a significantly smaller dose of thiopentone ($P < 0.01$; t test) than the other groups. Side effects were comparable in the three groups, but midazolam patients showed a significant degree of anterograde amnesia in four of the five tests, compared with temazepam and placebo patients. Temperature observations revealed a significant decrease in oral temperature in the medicated groups; before induction in midazolam patients ($P < 0.01$; t test), and at 1 h in both midazolam and temazepam patients ($P < 0.05$; t test). A reduction in oral temperature with temazepam has previously been demonstrated in a volunteer study (Pleuvry et al., 1980).

Although midazolam proved to be the superior premedicant drug, the delay in immediate and late recovery compared with temazepam would suggest that the latter benzodiazepine is more suitable for day-case patients. However, the quality of anxiolysis and amnesia produced by midazolam indicate that it would prove an excellent premedicant drug for inpatients, with high patient acceptability.

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EFFECT OF VERAPAMIL ON CALCIUM UPTAKE IN RAT DIAPHRAGM PREPARATION

F. A. WALI AND A. H. SUER*
Anaesthetics Unit, The London Hospital Medical College, London

The effect of verapamil on contractility of rat diaphragm in response to indirect stimulation, and uptake of calcium into unstimulated and stimulated nerve–muscle preparations, was studied to quantify the inhibitory effect of verapamil on calcium influx at the neuromuscular junction.

The preparation was set up in an organ bath containing Krebs–Henseleit solution 80 ml maintained at 38±2 °C and bubbled with 5% carbon dioxide in oxygen. Mechanical responses, elicited at 0.2–100 Hz with 5V (maximal) and 0.2 ms pulse duration, were recorded isometrically. Calcium uptake (µg/mg tissue min^{-1} and pmol mg^{-1} per impulse) was measured using the Technicon method, No. SG4-0080M84, the SMAC system, which is a computer-controlled biochemical analyser. The method is based on the work of Gitelman (1967), who modified the automated procedure of Kessler and Wolfman (1964), by incorporating 8-hydroxyquinoline to eliminate magnesium interferences. The calcium method uses the metal complexing dye (Cresolphthalein Complexone) to bind to calcium ions and to produce a pink coloured calcium dye with a maximum absorption at 570 nm. Repetitive nerve stimulation, at 0.2–100 Hz, produced frequency-dependent contractile responses; a mean maximum response of 3.5 ± 0.5 g was obtained with 28±2 Hz (mean±SEM; $n = 6$). The mean frequency which produced 50% maximum contraction (Freq._{50}) was 12±2 Hz. Verapamil 10 µmol litre^{-1} shifted, non-competitively, the frequency–response curve to the right such that mean Freq._{50} was not obtained. The mean IC_{50} value (concentration to produce 50% maximum inhibition) for verapamil 0.1–200 µmol litre^{-1}-induced inhibition of twitch tension was 65±5 µmol litre^{-1} ($n = 6$). Verapamil 10 µmol litre^{-1} reduced uptake of calcium into nerve–muscle preparations; higher reductions occurred at higher levels of nerve stimulation (table XVIII).

It was concluded that, by blocking calcium channels, verapamil reduced influx of calcium, and prevented its uptake at the rat neuromuscular junction. Similar results have been reported in the squid giant axon, using the photoprotein aequorin (Baker, Hodgkin and Ridgway, 1971).

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TABLE XVIII. *Blockade of calcium uptake produced by verapamil 10 µmol litre^{-1}, in a nerve–muscle preparation stimulated at different frequencies*

	Control (µg mg^{-1} min^{-1})	Verapamil (µg mg^{-1} min^{-1})	Block (%)	Control (pmol mg^{-1} impulse^{-1})
Unstimulated	1.5±0.1	1.36±0.1	9.3±0.7	
Stimulated at 0.2 Hz	1.82±0.2	1.09±0.05	20±2	0.7±0.1
Stimulated at 20 Hz	2.24±0.1	0.84±0.1	38±5	8.6±0.4
Stimulated at 50 Hz	2.63±0.4	0.35±0.1	74±3	4.0±0.2
Stimulated at 100 Hz	3.15±0.4	0.18±0.01	87±6	2.4±0.2

A COMPUTER CONTROLLED GAS MIXER

R. W. BOADEN, P. HUTTON AND C. R. MONK
Sir Humphry Davy Department of Anaesthesia, University of Bristol

A method of digital control of gas flow has been developed (Boaden and Hutton, 1984). In this paper a further development of the technique is described, encompassing computer control of both flow rate and mixing of anaesthetic gases, together with current uses.

The principles and construction of a prototype flow controller have been described fully elsewhere (Boaden and Hutton, 1986). In the present system the digital controller for each gas has been re-designed into a more compact unit. To construct a gas mixer, three separate controllers were built, one for each of the gases oxygen, nitrous oxide and air. Each controller provided a flow range of 50–12750 ml min^{-1} in 50-ml min^{-1} steps and the system allowed mixtures of air–oxygen or nitrous oxide–oxygen to be requested. Several safety features have been incorporated to the design; a nitrous oxide cut-off valve is operated from the oxygen supply; a manual oxygen supply is provided and in the event of power failure an automatic flow of 6 litre min^{-1} oxygen occurs. A simple rotameter gives a visual indication of flow, and pressure gauges are fitted for each gas. When the mixer is in use on patients, it is envisaged that both oxygen concentration and flow alarms be used.

Each of the individual digital valves was calibrated using a 1.5-litre capacity bubble flow meter. In the subsequent evaluation of the mixer, it proved difficult to measure flows greater than 7 litre min^{-1} with the bubble flow meter and gas mixtures precluded the use of rotameters. A 60-litre capacity gas collection bag was therefore used and timed volumes measured using an accurate gas-tight 1-litre syringe. For each combination of gases, two sets of tests were performed. One compared the desired flow rate as set on the computer (x ml min^{-1}) against measured flow rate (y ml min^{-1}) over a range of oxygen concentrations (21–100%). The other compared desired oxygen concentration (x% oxygen) against measured oxygen concentration (y% oxygen) over a range of flow rates (500–10000 ml min^{-1}). The oxygen concentrations were measured using a Servomex 570A Oxygen Analyser. The regression equations for the four sets of grouped results are shown (table XIX).

At present the gas mixer is being used in an experiment to implement feedback control of end-tidal carbon dioxide by means of continuous adjustment of the fresh gas supply to a Mapleson D system. Gas mixtures and flow rates are easily set from within a BASIC program.

TABLE XIX. *Regression equations*

Gas mixture	Regression	r	n
Flow rates			
Air/O_2	$y = 2.9 + 1.0x$	1.0	20
N_2O/O_2	$y = 5.9 + 1.0x$	1.0	20
% Oxygen			
Air/O_2	$y = -0.39 + 1.01x$	1.0	36
N_2O/O_2	$y = -0.06 + 1.0x$	1.0	32

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KETAMINE ANALGESIA IN YOUNG AND ELDERLY ADULT PATIENTS

W. WAY*, M. HOGER*, M. PRYOMSKI*, T. WARD* AND A. TREVOR*
Department of Anaesthesia/Pharmacology, University of California, San Francisco

It has been suggested that low doses of ketamine produce clinically useful analgesia (Sadove et al., 1971).

To evaluate i.v. ketamine as an analgesic for postoperative pain, 10 patients (18–45 yr) and nine patients (older than 70 yr) were studied after undergoing prosthetic orthopaedic surgery of the hip or knee. The pharmacokinetic profiles of i.v. ketamine were determined to detect any changes occurring with age.

In the recovery room the pain was evaluated using an analogue pain scale. When pain was moderate to severe by patient rating, ketamine hydrochloride 0.5 mg kg^{-1} or placebo was given as an i.v. bolus. Evaluations were then made for up to 2 h after drug administration or until the time when pain intensity returned to the moderate to severe level. The pharmacokinetic study involved blood sampling via a second i.v. catheter at 1, 2, 3, 4, 5, 10, 20, 30 and 60 min and at 1.5, 2, 3, 4, 6, 11 and 24 h after drug administration.

Ketamine produced maximum pain relief in the young group at 12.67 and 12.74 min in the older group. Severe pain returned at a mean of 22.1 min in the young group and at 30.4 min in the older group. Another measure of the duration of analgesia was the time between the dose of ketamine and that time when supplementary analgesic drug was used, which in the young group was a mean time of 28.1 and in the older group 37.1.

Although ketamine analgesia may be consistently demonstrated in a clinical pain model utilizing post-surgical patients, this analgesia is of short duration. This conclusion is supported by studies utilizing ketamine in an experimental pain model (Clements, Nimmo and Grant, 1982). Our pharmacokinetic data do not demonstrate significant differences in biodispositional parameters when examined in young and old patients (table XX).

TABLE XX. *Pharmacokinetic data*

Parameter	Elderly patients ($n = 7$)	Young patients ($n = 5$)
$T_{\frac{1}{2}}^{\alpha}$ min	4.1 ± 2.2	5.3 ± 3.7
AUC_0 (mg min ml^{-1})	25.1 ± 2.9	28.2 ± 3.1
Vd (litre kg^{-1})	3.51 ± 0.72	3.53 ± 0.96
Cl (ml min^{-1} kg^{-1})	20.2 ± 2.7	18.0 ± 2.3
$T_{\frac{1}{2}}^{\beta}$ (min)	119 ± 24	135 ± 29

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CORRESPONDENCE

DEADSPACE DURING HIGH FREQUENCY VENTILATION

Sir,—In the paper by Chakrabarti, Gordon and Whitwam (1986) on "the relationship between tidal volume and deadspace during high frequency ventilation" the authors present values for anatomical deadspace obtained from end-tidal P_{CO_2} (PE'_{CO_2}). At 15 b.p.m., tidal volume 400–500 ml, they obtained mean values for V_D^{anat} of 125 ml. The median value for what my colleagues and I have preferred to call the airway deadspace (V_D^{aw}) in an adult, chiefly male, population ventilated at 16–20 b.p.m. and similar tidal volumes was 83 ml (Fletcher and Jonson, 1984). The reason for the discrepancy between the two studies is to be found in Fletcher (1984) which Chakrabarti and his colleagues cite but do not heed. From that paper it can be deduced that a group of patients with a mean V_D^{aw} of 125 ml calculated from PE'_{CO_2} would have a true mean value of about 88 ml. Thus the value for V_D^{anat} at 15 b.p.m. in Chakrabarti's figure 2 is probably a gross overestimate. The next value, at 30 b.p.m., will also be an overestimate, although a lesser one since the error decreases with increasing frequency (f) (Fletcher, 1984).

When we come to values obtained at above 40 b.p.m., a new problem arises; the authors can no longer measure PE'_{CO_2}! Instead they reduce f and measure the PE'_{CO_2} of a breath at 30 b.p.m. Because the intrapulmonary distribution of gas varies with f, it is not certain that this is an acceptable way of finding what PE'_{CO_2} was at a higher frequency. (The fact that a good correlation was obtained between Pa_{CO_2} and PE'_{CO_2} is neither here nor there—the two will always be correlated.)

Thus the values given for V_D^{anat} are probably erroneous, and the paper would have gained in credibility by their omission. From a theoretical point of view, one cannot measure the *end-inspiratory* position of the alveolar/fresh gas interface by looking at an *end-expiratory* event (the arrival of end-tidal gas at the airway opening).

In the discussion section the authors state that "the single breath technique of measuring anatomical deadspace is also not free from assumptions, specifically in relation to phases II and III of the expired carbon dioxide curve and the unknown error caused by the inspiratory pause." I do not know what is meant by this, but one thing is clear. *Anatomical* considerations are of little interest; the real issue is the variable volume between the alveolar/fresh gas interface and the airway opening, for which V_D^{aw} is a logical term (Fletcher et al., 1981). The only way to measure this is with a single breath test. That the front moves during a breath hold or end-inspiratory pause may be bad news for anatomists, but that is how gas exchange works. It must be studied with the appropriate tools, and not with methodology described by Nunn (1977) as an undergraduate experiment.

A final point. Chakrabarti and colleagues mention Severinghaus and Stupfel's (1957) investigation of alveolar deadspace in dogs, in which the alveolar deadspace fraction was found to be relatively constant. However, as the latter point out, V_D^{aw} in their study was not correctly obtained, and therefore their alveolar deadspace values may be inaccurate. In our own work in patients (Fletcher and Jonson, 1984), the alveolar deadspace fraction increased as f increased, and tidal volume decreased, supporting the contention that intrapulmonary gas distribution changes with frequency. One wonders why the authors chose to cite a 29-year-old reference when more suitable modern ones are available.

R. FLETCHER
Lund

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Sir,—We wish to thank you for providing the opportunity of replying to Dr Fletcher's letter in response to our paper "Relationship between tidal volume and deadspace during high frequency ventilation" (Chakrabarti, Gordon and Whitwam, 1986).

It is surprising to us that Dr Fletcher appears to be contradicting his own statement (Fletcher, 1984). We quote the last sentence: "V_D^{Bohr} is representative of neither V_D^{aw} nor V_D^{phys}, but still has its place as an easily available non-invasive index of the efficiency of gas exchange." The measurement of V_D^{Bohr} was included in our paper as a matter of report, but the main thrust was on the physiological deadspace (V_D^{phys}). The errors involved in the measurement of anatomical deadspace (V_D^{anat}) were discussed. It would have been an easy option for us to exclude the measurement of V_D^{Bohr}. However, because of the interesting nature of the changes at different tidal volumes which parallel those of V_D^{phys}, and also the statement by Fletcher (1984) quoted above, we were prompted to include it in our paper. We also considered using the single breath technique, but apart from the technical difficulties, for example the response time of the available equipment, no one has yet shown that this technique can be applied for the accurate measurement of V_D^{anat} during high-frequency ventilation. It is also highly unlikely that this technique can be applied without any modification because of mixing of carbon dioxide in the anatomical conducting airways during high frequency ventilation. These considerations prevented us from undertaking measurements of V_D^{anat} by the single-breath technique, whereas V_D^{Bohr} is an accepted concept whatever it measures.

For us it has been a tragedy that, so far, all serious discussion of our paper, including that of Dr Fletcher (and the assessors for publication), has concentrated almost exclusively on the meaning of the Bohr-deadspace, in spite of the fact that it was clearly stated in our paper that such measurements were included merely as a matter of report. In so doing they have detracted from the main conclusion of our study—that is, the variability of the measured V_{D}^{phys} which appears to have a minimum value during HFV. V_{D}^{phys} is not of a fixed value, even in the same subject, but is a variable wasted ventilation volume which is a function, not only of anatomical structure or the pathological status of the pulmonary system, but also of the tidal volume, ventilation frequency and other parameters of the ventilation process and system. Further, this variable V_{D}^{phys}, which may be called "functional deadspace" for a particular ventilating process, has a minimal value which determines the tidal volume requirement to maintain carbon dioxide homeostasis during high frequency ventilation.

Turning to the point of our reference to the study of Severinghaus and Stupfel (1957) for comparison with our study, in preference to that of Fletcher (1984): in the latter study only two ventilation frequencies and tidal volumes were used, both of which are in the accepted normal range of conventional mechanical ventilation. In contrast, Severinghaus and Stupfel (1957) provided points down to small tidal volumes—which were more relevant to our study.

We hope that our study, which is the first of its kind in human subjects, will add to the understanding of the deadspace–tidal volume relationship during high frequency ventilation, thereby providing a more rational approach to the clinical application of this valuable new technique.

M. K. CHAKRABARTI
G. GORDON
J. G. WHITWAM
London

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HISTAMINE LIBERATION WITH ATRACURIUM

Sir,—I would like to comment on the case report of probable histamine liberation with atracurium by Lavery, Boyle and Mirakhur (1985). These workers administered an i.v. dose of atracurium 1 mg kg^{-1} which was nearly twice the upper limit of the recommended dose range 0.3–0.6 mg kg^{-1} (ABPI Data Sheet Compendium, 1985/6). It was not surprising, therefore, that a histaminoid reaction occurred, particularly as it has been demonstrated previously that doses of atracurium 0.9 mg kg^{-1} and greater will produce a transient arterial hypotension which is probably caused by histamine release (Hughes and Payne, 1983). Furthermore, Dr Lavery and his colleagues suggested that a dose of 1 mg kg^{-1} may be indicated where a rapid onset of block is desired. However, it has already been reported that, whereas the onset of block was shortened by increasing the dose of atracurium from 0.2 to 0.6 mg kg^{-1}, it was not shortened further when the dose was increased to 0.9 mg kg^{-1} (Hughes and Payne, 1983). Perhaps there is a finite time factor required for competitive blocking agents like atracurium to occupy the end-plate receptors, which is a relatively slow process.

R. T. OWEN
Crewe

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Sir,—We agree with Dr Owen that a 1.0-mg kg^{-1} dose of atracurium used in our case report (Lavery, Boyle and Mirakhur, 1985) was relatively large and would perhaps not be administered routinely as a single bolus. However, such a dose has been shown to produce complete neuromuscular block in about 2 min, which is significantly faster than the time of about 3.5 min obtained using a dose of 0.6 mg kg^{-1}, yet with a duration of clinical relaxation of less than 1 h (Mirakhur et al., 1985). The intubating conditions are consequently improved and doses of this magnitude would have an application in situations where relatively rapid intubation is required but the use of suxamethonium is contraindicated.

Obviously, one should weigh the possible advantages of a fairly rapid onset, but without a long duration of action, against the possibility of clinically important histamine release.

G. G. LAVERY
R. K. MIRAKHUR
Belfast

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INTRATHECAL MORPHINE AND MULTIPLE FRACTURED RIBS

Sir,—In his article, Kennedy (1985) described a patient in whom intrathecal morphine was used successfully to control the pain of fractured ribs. We have reviewed the notes of all the patients treated for chest injury on the Major Injuries Unit of the Birmingham Accident Hospital between January 1980 and December 1985. Approximately 20% of these patients were given intrathecal morphine.

It was apparent when intrathecal morphine was first used that the analgesia produced was often inferior to that achieved by the extradural administration of bupivacaine. The indications for its use have, therefore, been limited. Since 1980, 19 patients have received intrathecal morphine. Seven of these had fractures of the first and second ribs; seven had other painful injuries which also required powerful analgesia; thoracic extradural analgesia was technically impossible in two, and the remainder had cardiovascular problems and were thought to be unsuitable candidates for thoracic extradural analgesia.

In addition to the provision of adequate analgesia to permit painless deep breathing, coughing and physiotheraphy, our policy for the management of chest injuries is similar to that detailed by Kennedy, namely restriction of crystalloid fluids, maintenance of a normal circulating blood volume with colloidal solutions or blood, and humidification and oxygen enrichment of inspired air.

Four of the 19 patients developed respiratory failure necessitating mechanical ventilation within 24 h of the use of intrathecal morphine. Of the remaining 15, 10 required more than one dose. The mean time between doses was 30 h (range 9–72 h). The time between doses did not correlate with dosage, which was between 1 and 2 mg depending on the size and age of the patient. In spite of appropriate dosage, analgesia was inadequate in 27% of patients. Nine patients suffered one or more complications attributable to the intrathecal morphine. The incidence of complications was as follows: post-spinal headache (6.6%), excessive drowsiness (26.6%), respiratory depression as indicated by $Pa_{CO_2} > 7$ kPa (13.3%) and nausea (20%). Urinary retention occurred in four of the 11 patients who were not catheterized on admission. One patient became profoundly hypotensive after the first dose of intrathecal morphine and was thought to have had a myocardial infarction. This was not confirmed by ECG or changes in enzyme concentrations and the hypotension was attributed to the morphine. No patient developed pruritis, although one complained of numbness of the chest wall, which he found an unpleasant experience. There were no cases of anxiety, hallucinations or meningitis.

Five patients received three or more doses. Three patients complained that after the third dose the pain relief was less effective than after previous doses. Two were given a fourth dose of intrathecal morphine less than 12 h after the third and one patient was given alternative analgesia.

There is no doubt that intrathecal morphine is a useful method of pain relief in the type of patient described. However, we believe that, in the absence of contraindications, thoracic extradural analgesia using bupivacaine is the analgesic method of choice for chest injuries, as the pain relief is superior. The only potentially serious complication in a far greater number of patients had been arterial hypotension, which has been easily and rapidly corrected by infusing plasma or blood.

G. R. Dickson
Anne J. Sutcliffe
Birmingham

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USE OF ATRACURIUM IN PRE-ECLAMPTIC PATIENTS

Sir,—Laudanosine, one of the metabolites of the Hoffmann degradation of atracurium, has been shown to produce central nervous system excitation in a variety of laboratory animals (Lanier, Milde and Michenfelder, 1985). Shi and colleagues (1985) have shown that central nervous system excitation by laudanosine can increase the minimum alveolar concentration of halothane in rabbits up to 30%. These central nervous system excitatory effects were not considered to be of concern because of low anticipated blood concentrations of laudanosine during the clinical use of atracurium. However, recently, Fahey, Rupp and Canfell (1985) showed that a significantly greater plasma concentration of laudanosine could be achieved following a single bolus dose of atracurium 0.5 mg kg^{-1} in the presence of renal failure.

The pre-eclamptic patient may have pathology involving a variety of major organs (Wright, 1983). It is not uncommon to see hepatic injury and renal insufficiency in the severe pre-eclamptic patient. Increased central nervous system irritability is of special concern and is, indeed, the hallmark of the disease. The aetiology of eclamptic seizures remains unclear.

At our institution, more than 200 Caesarean sections, in patients including 12 women with severe pre-eclampsia, have been performed using atracurium without any observed adverse side-effects. We are also unaware of any reports of seizures in the parturients in whom atracurium was used. Nevertheless, with the knowledge that laudanosine possesses central nervous system excitatory effects and convulsant properties in laboratory animals, and the fact that the pre-eclamptic patient can develop seizures in the period immediately postpartum, we believe it may be prudent to reconsider the use of atracurium in the pre-eclamptic patient.

R. A. Fujita
H. J. Choi
Orange, California

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Wright, J. P. (1983). Anesthetic consideration in pre-eclampsia-eclampsia. *Anesth. Analg.*, 63, 590.

Sir,—Drs Fujita and Choi's comments on observations in pre-eclamptic women raise an important clinical issue with respect to the potential toxicity in man from laudanosine. First of all, it should be stated that animal studies indicate that doses of laudanosine necessary to produce seizures are unlikely to be reached in patients receiving atracurium for surgical relaxation. Second, patients receiving volatile anaesthetics and, in particular, severe pre-eclamptic patients on magnesium sulphate therapy are likely to be protected from the central nervous system (CNS) stimulation produced by laudanosine. In the final analysis, there still is much that we do not know about the action of laudanosine in man. Until more is known from studies looking for CNS effects of laudanosine in anaesthetized patients, the clinician should use his own judgement, as Drs Fujita and Choi have done, and reserve the use of atracurium to situations where its use is clearly indicated (such as severe metabolic organ disease).

M. R. Fahey
San Francisco

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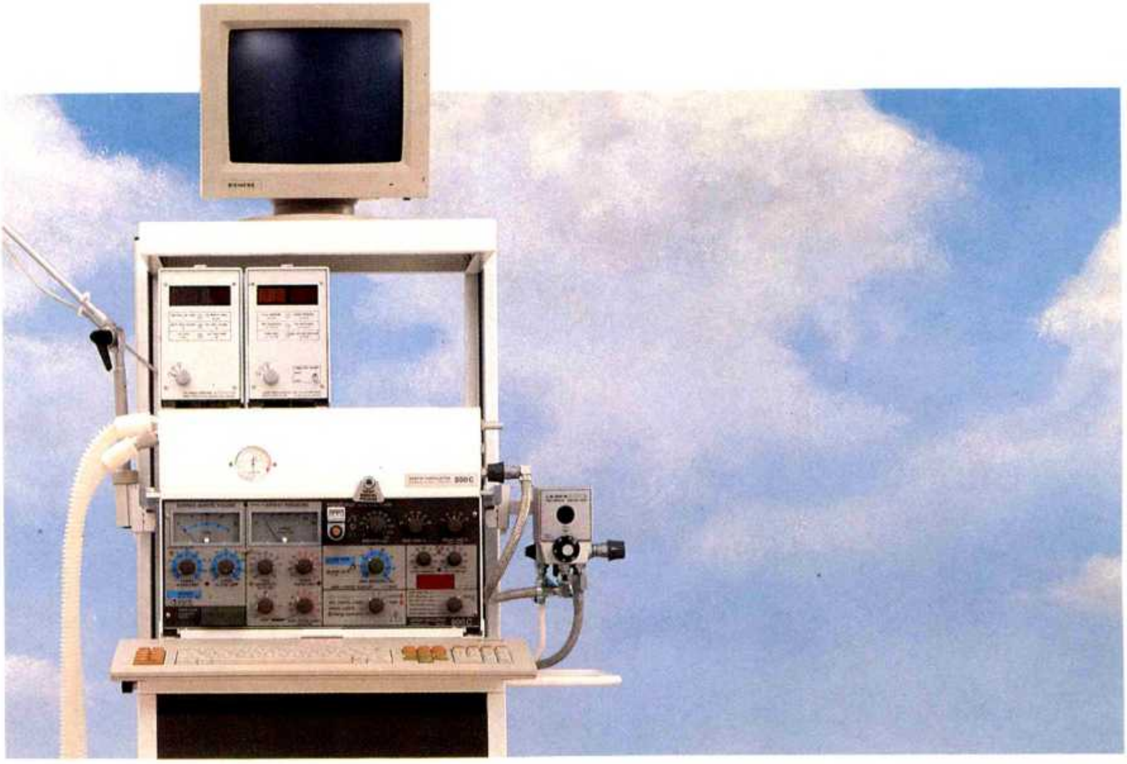

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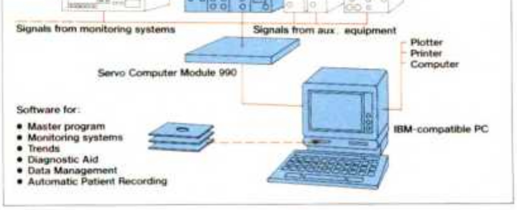

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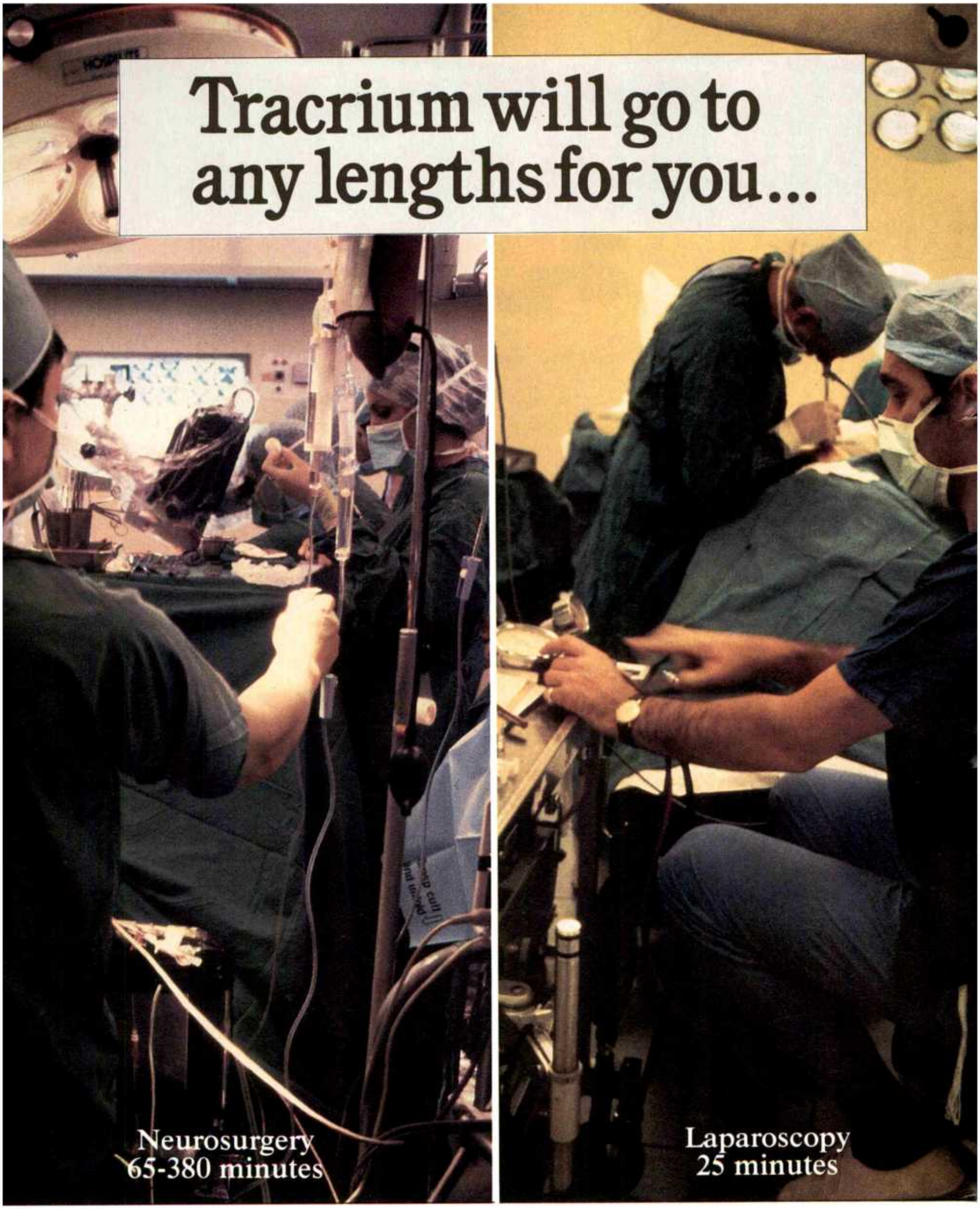

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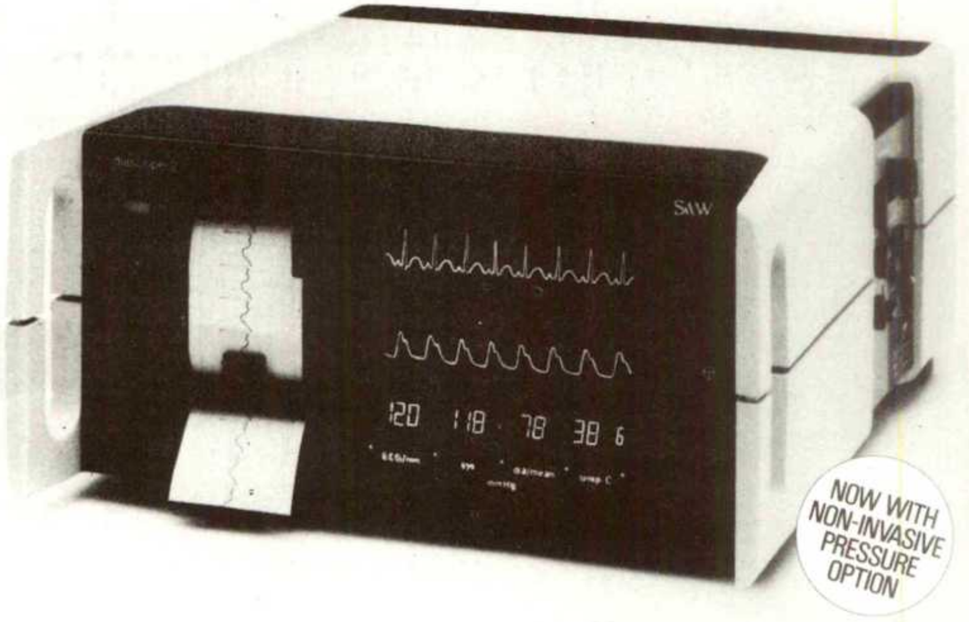

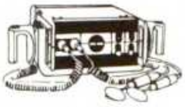
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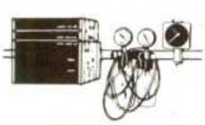
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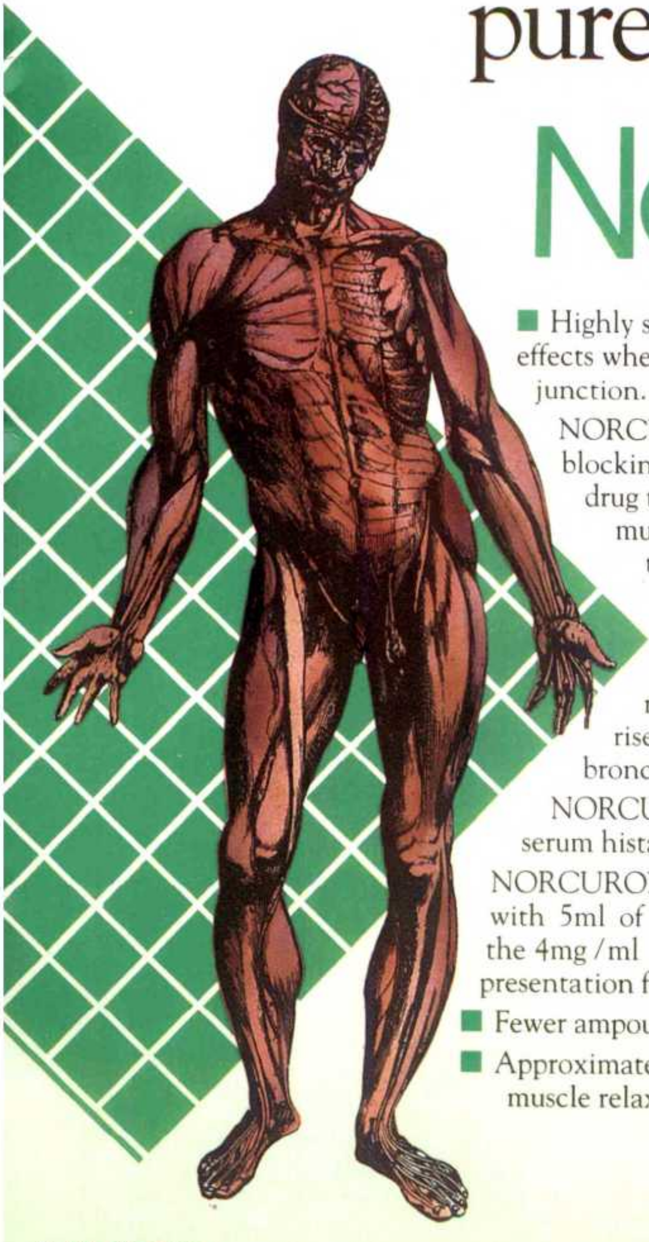

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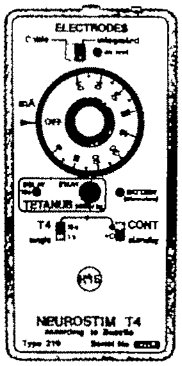

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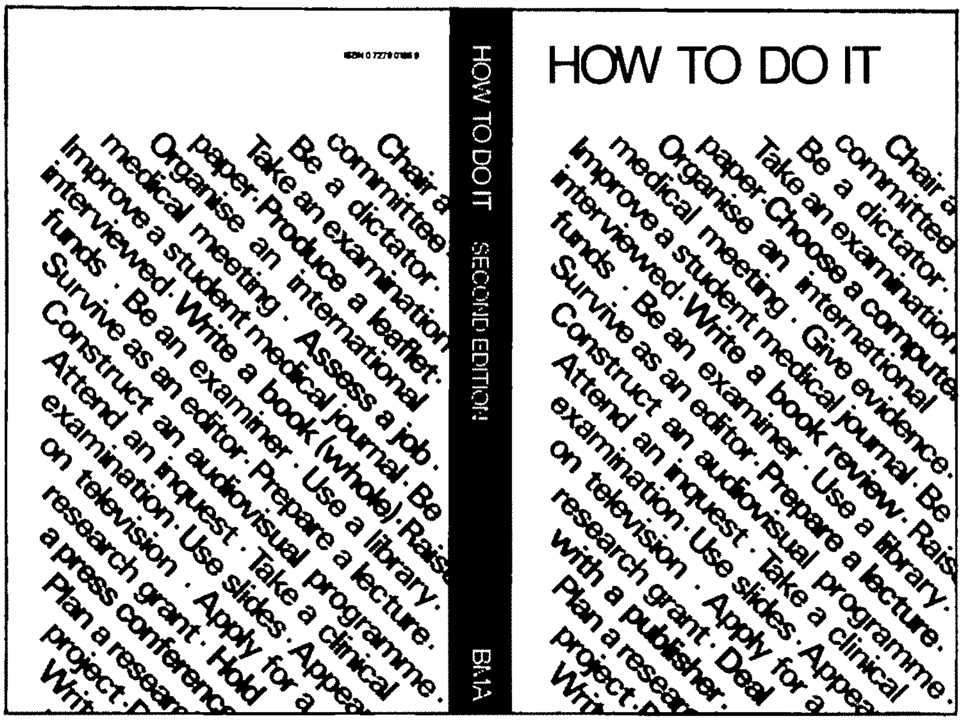
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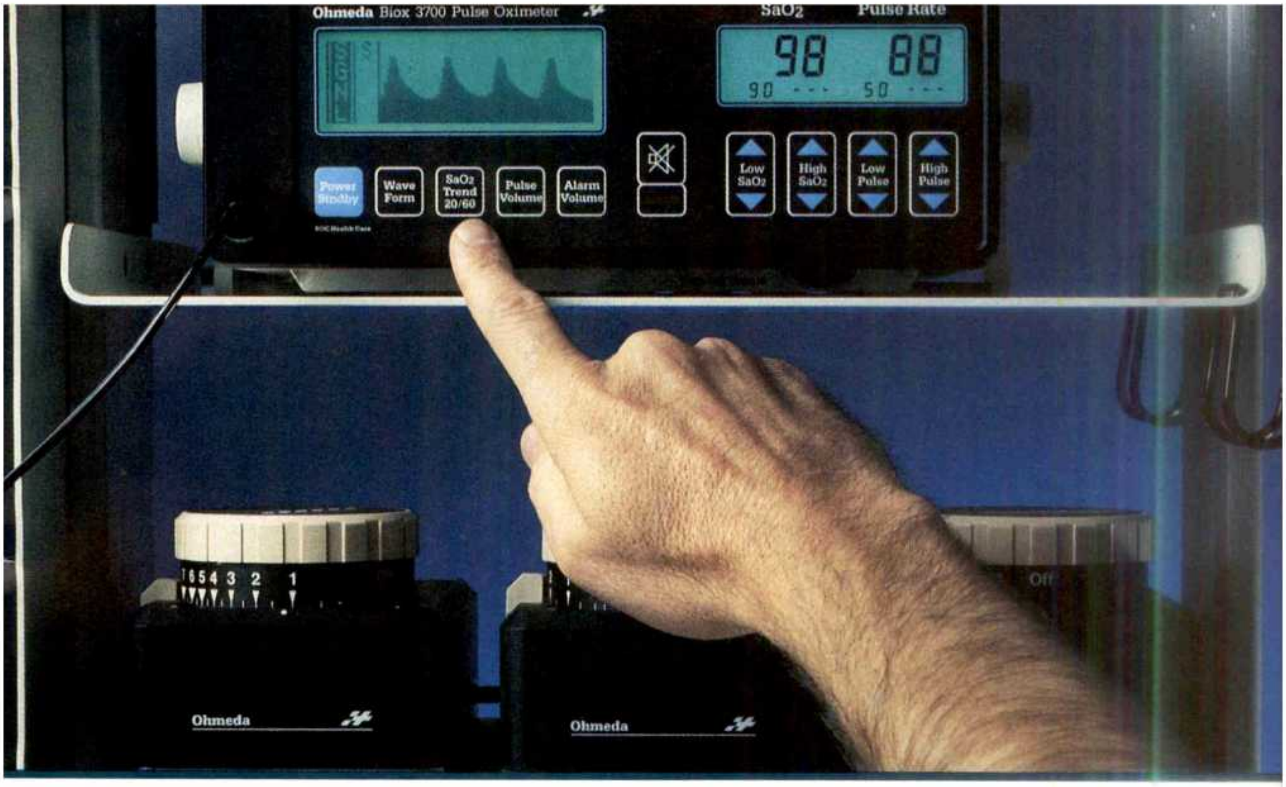

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ERRATUM

Br. J. Anaesth. (1986), **58**, 779

The sentence that begins on line 29, page 786, should read as follows: "It is now established that the most suitable agent is prilocaine, which causes minimal systemic toxicity should it leak out into the circulation." The rest of the sentence should be deleted.

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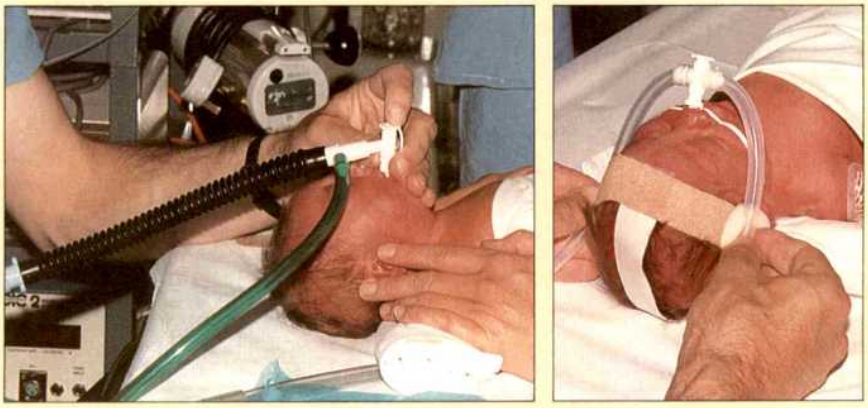

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 58, No. 12 DECEMBER 1986

EDITORIAL

LET US BE CLEAR

We should modify Montaigne's sentiment that heads the editorial page of the *British Journal of Anaesthesia*. It should read "I would have everie man write what he knowes and no more—but write it well." There would be many good reasons for changing writing habits even if the readers of our journals were confined to the British Isles, but the anaesthetic community is now world-wide and English is not a first language of many of those who read our literature. This makes it even more important that our writing is clear and unambiguous.

A number of things make it currently appropriate to think about written English. First, there is the increasing likelihood that all anaesthetists will write something. Halsey (1985) argued very effectively that experience in scientific discipline is an important part of the training of anaesthetists. The experience of the discipline is probably of more benefit than the ability to produce a piece of original research, but nevertheless for some time an applicant for a consultant post has been expected to have publications in his curriculum vitae. The recent increase in popularity of anaesthesia as a career has meant that this is also becoming true at the lower step, from registrar to senior registrar. Whether or not this is desirable in itself is a point for further discussion, but, especially as some of these registrars will, one hopes, continue their research interests and form the University Departments of the future, it would be a very useful contribution if they were to help to alter many of the undesirable patterns of writing that seem self-perpetuating in anaesthetic papers.

We need to communicate not only with fellow anaesthetists but, as a profession, we need to communicate with the public. Lock (1985) laments the way we present our public image. In a time of financial stringency and medical audit we cannot afford to stand on our dignity, pleading erudition; if we make a start by deflating the pomposity of much of the medical reporting within the profession, then we will be better qualified when we need to present our case to those outside the profession—including the media.

The feeling that there is room for improvement has already been voiced in the general medical press. Dr Michael O'Donnell, in his regular (and well-written) column in the *British Medical Journal* "One Man's Burden", was concerned "at doctors' declining ability to express their ideas in clear uncluttered prose" (O'Donnell, 1985). He quoted writing of John Snow to illustrate clear, direct medical prose; with that example, we anaesthetists should have the stimulus to try harder.

Here, with apologies to the authors, are two contrasting samples of prose from an anaesthetic journal; they are the opening sentences of two research papers on malignant hyperpyrexia. The first is "Malignant hyperthemia (MH) is a rare, but serious, complication of anaesthesia with a high mortality rate." It is short, sharp, and conveys its meaning clearly. It would be a good start for a candidate in the examination for the F.F.A.R.C.S.

The second sentence is "Predisposition to malignant hyperpyrexia (MH) is encountered as a dominant pharmacogenetic abnormality in a small proportion of patients undergoing anaesthesia with a variety of commonly used anaesthetic agents." This is longer than the first sentence, but actually adds little. It is ambiguous, because one could infer from the final phrase that, for the syndrome to occur, a number of agents needed to be given during a particular anaesthetic. MH is the *result* of a genetic abnormality, the anaesthetist does not really encounter it as such; it is encountered, together with other features of the syndrome, as a progressive increase in temperature.

These criticisms are only of the writing of these sentences, taken out of context, and do not imply any judgement of the complete papers, either of the style or of the scientific content, but there are whole papers written in this circumlocutory fashion. O'Donnell (1985) calls it pseudo-dignification.

If we are to improve matters, then first we must recognize that there is a problem. Supervisors of research projects, and those to whom junior anaesthetists bring their written reports, must be prepared to look at the way articles are written, as well as what is written. If we write English, then we should read English: that will increase our awareness of good writing. It is a cardinal error to think that scientific writing is in any way different from the writing of English in any other field—except that it will contain technical terms. O'Donnell (1985) supports Woods (1984) in suggesting that well-written modern novels are a good source of clear writing. Whale (1984) uses extracts from modern novels to illustrate the features of good prose; his book is easily read in an evening.

Closer to medicine, an anthology of the writings of Richard Asher has just been reprinted by the British Medical Association (Asher, 1984) and has been advertised in the *British Journal of Anaesthesia*. As a preacher by example, he can have few equals, and I would direct to pages 83–4 of the anthology anyone who feels that to fuss about style is unnecessary.

As with any skill, one learns by example and practice. A most welcome innovation has been the recent workshop on medical writing organized by this Journal. That is a start and, if those who attended disseminate the message, then we shall all be the better for it.

N. W. Goodman

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EDITORIAL

ACKNOWLEDGEMENTS

Each manuscript submitted to the *British Journal of Anaesthesia* is reviewed, not only by members of the editorial staff, but also by individuals not associated with the editorial staff who have particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaesthesia. Acceptance for publication is, consequently, based on the views of two or more individuals as to the originality, validity and clinical relevance of the information presented. The Editor would like to acknowledge sincerely the significant contributions made by the undernoted individuals who, in addition to the members of the Editorial Board, reviewed manuscripts during 1986.

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Br. J. Anaesth. (1986), 58, 1348–1356

NITROUS OXIDE AND THE FETUS

A Review and the Results of a Retrospective Study of 175 Cases of Anaesthesia for Insertion of Shirodkar Suture

L. M. ALDRIDGE AND M. E. TUNSTALL

SUMMARY

The outcome of 175 pregnancies during which nitrous oxide was administered has been evaluated. All anaesthetics were of short duration (20–30 min) and 97% were administered during the second trimester. No adverse effects were identified. The mechanism of potential toxicity and the implications of the use of nitrous oxide during the first and second trimesters of pregnancy are discussed.

Nunn and Chanarin (1985) have drawn attention to the fetotoxicity of nitrous oxide in animal studies and suggested that its use as an anaesthetic, in the first and second trimesters of human pregnancy, may constitute a potential hazard.

As a consequence, the use of nitrous oxide in pregnancy has been abandoned by a number of centres in the U.S.A. (Marx, personal communication).

During the 8 weeks of embryogenesis the organism is at its most vulnerable to mutagenic influences and, in recent years, there has been increasing awareness of the aetiological role that environmental toxins, infective agents and drugs may have on the development of congenital abnormalities. Many common congenital malformations have a multifactorial basis and a hereditary predisposition may be precipitated by such factors of which drugs, including anaesthetic agents, are among the most readily identifiable (Pedersen, Morishima and Finster, 1985). Avoiding risk attendant upon exposure is rendered difficult by the inability to confirm or even suspect pregnancy in its initial stages.

The organism remains at risk during the fetal stage of development, but acute exposure is less likely to prove damaging. Several studies have examined the effect of chronic exposure of operating theatre staff to low concentrations of anaesthetic agents including nitrous oxide.

The majority of studies have identified an increased risk of spontaneous abortion in exposed personnel (Cohen, Bellville and Brown, 1971; Knill-Jones et al., 1972; Spence and Knill-Jones, 1978; Tomlin, 1979; Buring et al., 1985). However, it has been found that the abortion rate in anaesthetists is not significantly higher than for other hospital doctors (Spence, Knill-Jones and Lawne, 1982) and Pharoah, Alberman and Doyle (1977) were unable to show any increased risk of abortion.

The positive findings of an increased incidence of fetal abnormalities presented by Corbett and colleagues (1974) and Tomlin (1979) have not been confirmed in the prospective trial of Spence, Knill-Jones and Lawne (1982). Although correlation between the blood and atmospheric concentrations of nitrous oxide has not been observed consistently, it has been demonstrated that assiduous scavenging can result in 90–95% reduction in blood concentrations in theatre personnel (Krapez et al., 1979); with the increased awareness of the problem, the scavenging of exhaled gases may be more commonly used by anaesthetists who are pregnant.

The adverse effects of nitrous oxide on cellular metabolism have been reviewed (Healy, 1981).

LOUISE M. ALDRIDGE,* F.F.A.R.C.S., D.C.H.; M. E. TUNSTALL, M.B., B.S., F.F.A.R.C.S., D.OBST.R.C.O.G.; Department of Anaesthetics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB.

* Present address, for correspondence: Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW.

Since 1956 it has been appreciated that nitrous oxide can be toxic to the haematopoietic tissue of man (Lassen et al., 1956). This toxicity is ascribed to interference with folate metabolism. The cyclic nature of the pathways in which folate co-enzymes function as acceptors and donors of single carbon units has been reviewed (Brody, Shane and Stokstad, 1984).

Detailed consideration of the inactivation of methionine synthase by the oxidation of its co-factor vitamin B_{12} (Deacon et al., 1978; Koblin et al., 1981) and the subsequent perturbation of thymidine synthesis by the derangement of folate metabolism has been described elsewhere (Amess et al., 1978; Chanarin, 1980).

It has been suggested that nitrous oxide may also impair RNA production by affecting purine synthesis indirectly in depleting the production of formate (Nunn and Chanarin, 1985).

In addition to the haemopoietic effects, an increased number of abnormalities of the ribs and vertebrae with increased absorption of male embryos has been documented when pregnant rats were exposed to 50% nitrous oxide for 2–6 days commencing at day 8 (Fink, Shepard and Blandau, 1967). These observations were confirmed and additional abnormalities described when 70–75% nitrous oxide was administered for 24 h to rats on the 9th day of pregnancy (Lane et al., 1980; Lane et al., 1981).

Similar findings in other animal species (Smith, Gaub and Moya, 1965; Shah, Burdett and Donaldson, 1979) have confirmed the mutagenic potential of nitrous oxide. The prevention by folinic acid of some of the teratogenic effects in rats suggests that similar interference with folate metabolism is responsible for these as well as for the haemopoietic effects (Halsey et al., 1985).

Procedures undertaken in very early pregnancy may result in spontaneous abortion (Smith, 1963), the aetiology of which must remain speculative. From the confirmation of pregnancy to the end of the first trimester, elective surgical procedures are unusual. The commonest elective operative procedure during pregnancy is the insertion of Shirodkar suture which, however, in Aberdeen is rarely undertaken before the commencement of the second trimester.

To determine whether any significant risk of congenital abnormality is associated with this procedure, the outcome of the pregnancies of 130 women delivered between 1978 and 1984 were examined in detail, and compared with those of the background obstetric population (Hall et al., 1985).

PATIENTS AND METHODS

The records of all the patients presenting for insertion of Shirodkar suture in the period 1978–1984 were traced.

The mother's records were examined, details of past obstetric history, the type of anaesthetic used, outcome of pregnancy and any abnormalities at birth noted.

Since Aberdeen has a stable population with a single maternity record department and a single children's record department serving the area, it was possible to follow up all the children's records, and note any abnormalities. The timing of the insertion of the suture in relation to gestation was noted. All third trimester procedures were excluded.

RESULTS

During the period 130 women were identified who required the insertion of a Shirodkar/McDonald

TABLE I. *Indications for insertion of Shirodkar/McDonald suture*

	Total No. of patients	No. of pregnancies				Total No. of cases
		1	2	3	4	
No previous abortion						
Cone biopsy	5	5				5
Premature cervical opening	15	11	3	1		20
Previous abortion						
First trimester	18	15	3			21
First and second trimester	46	26	18	1	1	69
Second trimester	46	33	12	1		60
Totals	130	90	36	3	1	175

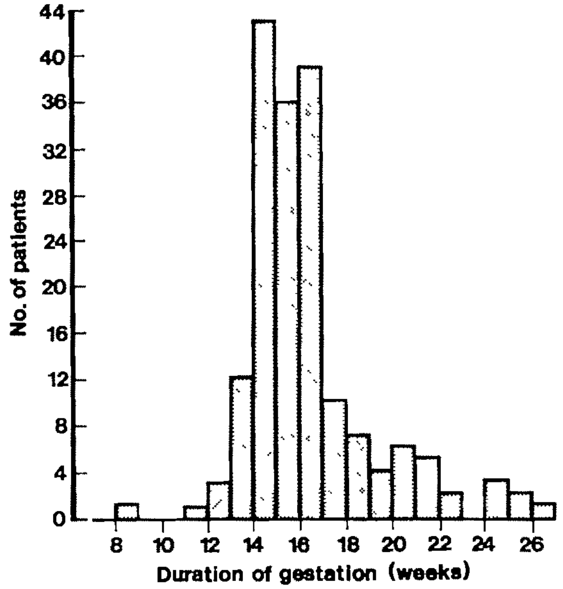

FIG. 1. Weeks gestation at Shirodkar/McDonald suture insertion.

suture for one or more pregnancies. All had received nitrous oxide as one component of a general anaesthetic technique.

All the women were parous, 110 having a history of previous abortion(s) (table I). In this group there was a total of 94 first trimester and 132 second trimester abortions in the past obstetric history. A total of 175 occasions were identified when nitrous oxide has been used during the first two trimesters of pregnancy.

Eight patients were receiving folic acid supplements at the time of the anaesthetic.

Figure 1 details the timing of the procedure: 67.4% of the Shirodkar/McDonald sutures were inserted between 14 and 16 weeks.

Table II compares the age, smoking habits, parity and spontaneous preterm delivery rate with the background obstetric population (Hall et al., 1985).

Figure 2 abstracts the outcome of each of the pregnancies. Of the 176 babies (one set twins) 151 were normal, six had minor abnormalities, four had major abnormalities. There were 11 abortions and four stillbirths or premature neonatal deaths.

In addition a number of abnormalities of doubtful significance were noted:

1 small pigmented naevus on leg—excised at birth
1 small haemangioma developing at 6/52 in a preterm baby
4 small hydroceles which resolved spontaneously
3 mild positional talipes calcaneovalgus
1 very mild positional talipes equinovarus
1 mild metatarsus varus
5 "clicking" hips all of which were normal without treatment when seen at 1-month-old at the hip clinic.

TABLE II. *Characteristics of patients in the series; comparison with background population*

(1)	Age (yr)	14–19	20–29	30+
	Total No.	6	94	76
	%	3.4	53.4	43.1
	Background (%)	11.4	70.8	17.8
(2)	Parity	0	1–2	3+
	Total No.	—	74	102
	%	—	42	58
	Background (%)	45	51	4.0
(3)	Smoking cigarettes (No./day)	0	1–10	11+
	Total No.	97	25	54
	%	55.1	14.2	30.6
	Background (%)	55.1	15.4	29.5
(4)	Spontaneous preterm delivery (Parity)	0	1–2	3+
	Total No.	—	11	19
	%	—	14.8	18.6
	Background (%)	5	3.6	6.5

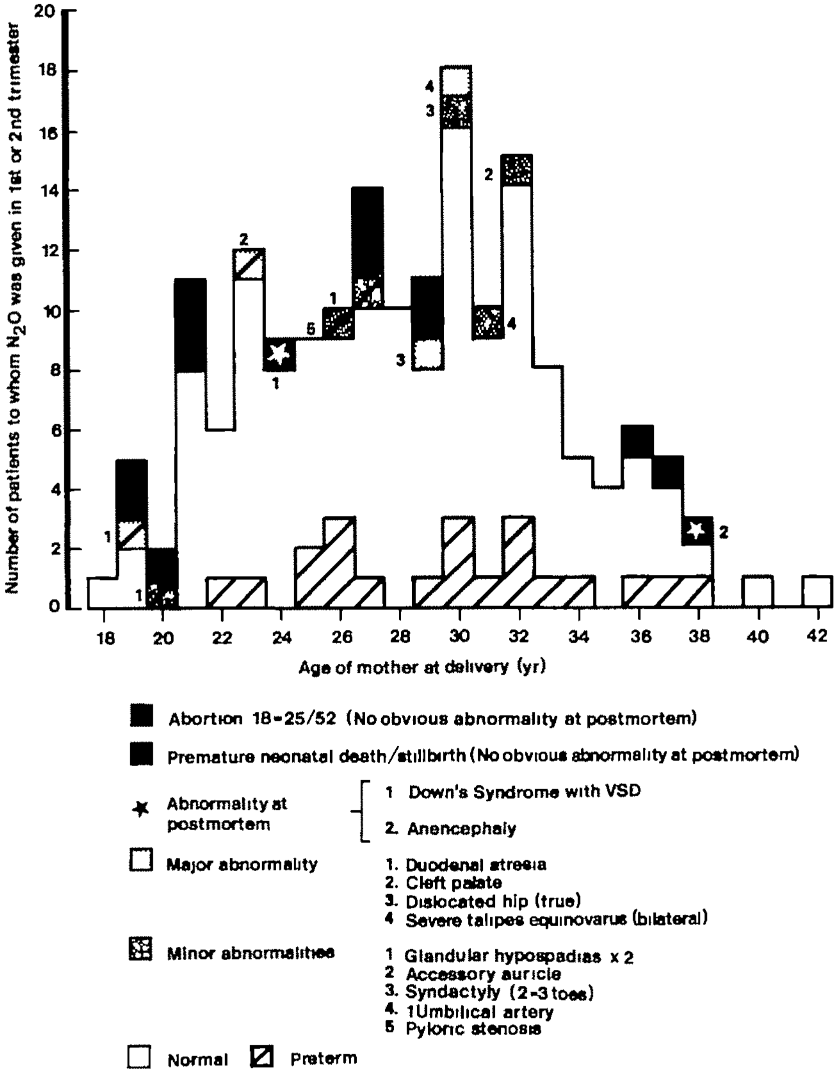

FIG. 2. Outcome of pregnancy and age of mother at delivery.

Table III lists the more significant abnormalities with relevant details of the obstetric history where appropriate, the embryological timing of the malformations and the incidence of the condition.

DISCUSSION

Compared with the background population the patients in this study are a high-risk obstetric group. The women were significantly older (42.6% being older than 30 yr) with a significant increase in the overall parity represented by 57.8% of the women having a parity of 3+. The increase in parity arose from the large numbers of first and second trimester abortions and previous premature neonatal deaths. As can be seen from the comparison of maternal characteristics, there was strikingly little difference in the smoking pattern.

Not surprisingly, in a group of women who by definition are unlikely to carry a baby to term, the spontaneous preterm (less than 37 weeks) delivery rate was approximately three times the average for all parities.

There were 28 premature babies, many of

TABLE III. *Abnormalities with associated maternal and known embryological/aetiological factors. LB = Live birth; A = abortion*

		Past obstet. history		Baby				
Abnormality	Maternal age (yr)	LB	A	Weeks gestation at birth	Sex and birth weight	Suture inserted (gestation weeks)	Embryological development complete/aetiology (gestation weeks)	Incidence
Duodenal atresia	19	0	3	28	F. 1320 g Forceps	13	10	1 in 10000 (Fonkalsrud, 1979)
Cleft palate	23	0	2	29	F. 1320 g SVD	13	12	1.7 in 1000 Varies with race Increased if family history (Cole, 1983)
Glandular hypospadias	20	1	0	36	M. 2620 g SVD (no op. required)	24	14	4 in 1000 (Cole, 1983)
	27	0	2	32	M. 1760 g SVD	18		
Accessory auricle	32	2	0	40	M. 3000 g SVD	16	8	None available
Syndactyly	30	1	3	40	F. 3180 g SVD Mild, 2nd & 3rd toes	14	10	2.7 in 1000 Autosomal dominant (Cole, 1983)
Single umbilical artery	31	1	2	40	M. 3360 g SVD No other abnormality	14	8 ? Possible atrophy	1 in 100 (Monie, 1970)
Congenital dislocation of hip	29	1	2	40	F. 3450 g SVD Adductor tenotomy	14	Last 4 weeks of pregnancy ? Maternal hormones	1.8 in 1000 M:F 1:4 (Mackenzie and Wilson, 1981)
Talipes equinovarus	30	1	2	40	M. 3520 g Forceps Soft tissue release	13	Genetic and environmental	4 in 1000 Increased for sibs M:F 2:1 (Millen, 1963)
Pyloric stenosis	26	0	1	34	M. 2080 g LUSCS	11	Polygenic	4 in 1000 Grampian Computer Services

whom experienced initial respiratory, electrolyte and nutritional problems, resulting in two neonatal deaths. Developmental review of the survivors at term + 10 months was normal except that, within this group, two of the major and three of the minor abnormalities were identified (fig. 2).

One stillbirth was found to have Trisomy 21, and the gestation of an anencephalic fetus was terminated at 26 weeks. These were the only two known abnormalities among the 13 fetal deaths and their known genetic and embryological origins had occurred before the administration of nitrous oxide. The overall incidence of abnormalities in this study (6%) accords with the Scottish norm (6%) (Cole, 1983). However, geographical variation of some conditions occurs and in a study of this size difficulties exist in undertaking meaningful statistical analysis and it is rendered necessary to consider in detail all the tabulated abnormalities in order to determine the possible aetiological role of nitrous oxide in their development.

Nos 1–5. Five abnormalities are known to arise from defective embryogenesis occurring before the administration of nitrous oxide (Millen, 1963; Moore, 1977).

No. 6. Single umbilical artery is one of the commonest malformations in man. Although frequently associated with other malformations (Froehlich and Fujikura, 1973), it was in this instance an isolated finding. One case in 176 is within the expected incidence of 1 in 100 (Benirschke and Bourne, 1960). Whilst a single umbilical artery may result from aplasia or atrophy of the missing vessel, it may also arise from persistence of the normally transient single umbilical artery of the 4–5 week embryo (Monie, 1970). Consequently, it is probable that this abnormality existed before the anaesthetic.

No. 7. The aetiology of congenital dislocation of the hip almost certainly involves more than one factor. In 2.7% of cases it occurs in conjunction with other musculo–skeletal abnormalities (Artz et al., 1975), but as an isolated phenomenon develops within the last 4 weeks of intrauterine life. An association is postulated with an overspill of maternal hormones (Barlow, 1968).

There were five cases of "clicking" hip identified on examination 24 h after birth. Untreated, all were normal when seen at 3–4 weeks old at the hip clinic. In Aberdeen there is an incidence for 1 in 20 for such suspected abnormality of the hips (MacKenzie and Wilson, 1981).

The incidence of true congenital dislocation of the hip (CDH) requiring operation is 1.8 in 1000 (MacKenzie and Wilson, 1981), with female preponderance four times that of male (Artz et al., 1975). The one true CDH in a female child does not allow adequate statistical comparison in a series this size, but in view of the believed late onset of the condition it appears unlikely to be associated with nitrous oxide given at 14 weeks gestation.

No. 8. There is a variable incidence of 1 in 800 to 4 in 1000 reported for talipes equinovarus (Millen, 1963; Wynne-Davies, 1964), with a 2:1 male to female ratio and an increased incidence in siblings.

The aetiology is complex with a mixture of both environmental and genetic factors (Wynne-Davies, 1964). However, two predominant types are identified. The one which is mobile and readily manipulated is thought too be caused by extrinsic intrauterine forces. The other more rigid variety is the result of an intrinsic developmental abnormality of connective tissue (Sharrard, 1979).

Although commoner in girls, the incidence of talipes calcaneovalgus and metatarsus varus is similar to talipes equinovarus. Many cases go unrecorded as the deformity usually disappears so that the true incidence is higher than that reported. There were three cases of mild positional talipes calcaneovalgus and one case of metatarsus varus in this series. Although this is slightly above the reported incidence, it seems unlikely that the nitrous oxide was responsible.

No. 9. Pyloric stenosis is a polygenic condition and is the commonest cause of abdominal surgery in infancy (Carter and Evans, 1969). It has an overall incidence of 1 in 250 births. One case in 176 is within that expected for the group.

There is no evidence from the data obtained in this study to suggest that short-term exposure to nitrous oxide in the second trimester of pregnancy was associated with an increased incidence of fetal malformations.

A comparison of the composite major temporal landmarks of embryological development in rat and human (fig. 3) indicates that the work of Fink and co-workers involved prolonged exposure of developing rat embryos at a critical phase of organogenesis. Indeed, applying strict correlation,

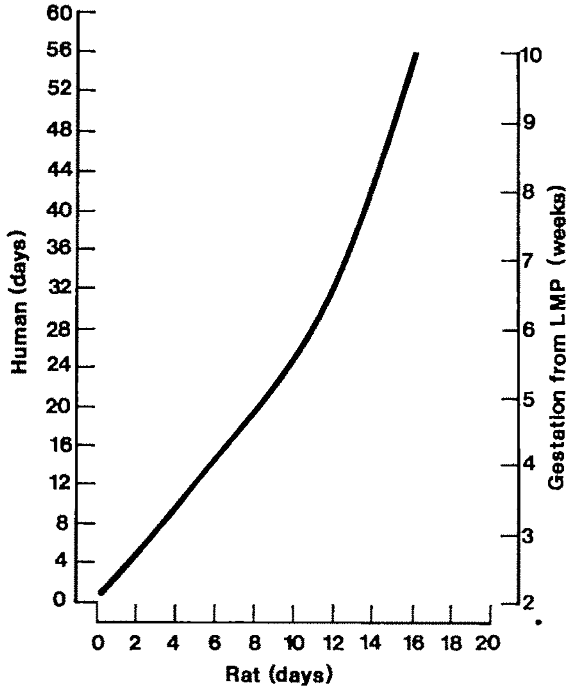

FIG. 3. Time scale of embryological development: comparison of rat and human; a composite of major temporal landmarks. (Data abstracted, for human from Moore (1977) and for rat from Beaudoin (1980).)

the shortest period corresponds in the human to exposure from day 19 to day 23 post conception (4.5–5.25 weeks from LMP) and the longest from day 19 to day 40 (4.5–7.75 weeks from LMP).

It is of note that the folic acid requirement for the rat, so far as can be determined, is between 5 and 20 μg day^{-1} compared with 50 μg day^{-1} in the adult non-pregnant human (Brody, Shane and Stokstad, 1984).

Methotrexate and aminopterin are folic acid antagonists which bind to dihydrofolate reductase, thereby blocking folate metabolism. As abortifacients they were administered between 6 and 10 weeks gestation and their teratogenic properties have been known since 1950. In five reported cases in which pregnancy continued, the infants suffered major cranial and skeletal abnormalites (Stevenson, 1973).

Folate is the only vitamin for which the requirement doubles in human pregnancy—mainly during the last trimester. However, periconceptual shortage (*viz.* 28 days after ovulation) may be implicated in the aetiology of neural tube defect (Truswell, 1985); the latter remains controversial, as does the safety of folic acid supplementation (Lancet, 1982).

In any event, the results of this study were not obscured by the concomitant administration of nitrous oxide and folate supplementation as it is the policy of the obstetric senior staff committee in Aberdeen to give iron and folate only when clinically indicated and only eight patients were receiving folic acid at the time of the procedure.

Nitrous oxide, in common with most inhalation agents, alters the dynamics of uterine blood flow. It is also known that nitrous oxide non-selectively facilitates pulmonary transepithelial transport and it is suggested that uptake of a variety of inhaled toxic factors may be increased (Gordon, 1985). Although it has also been postulated that competitive inhibition of oxygen binding occurs (Ebert and Hornsey, 1958), the burden of the presently available evidence is that the adverse embryological effects arise from impaired DNA synthesis.

The known inefficient utilization of folic acid in vitamin B_{12} deficient animals is believed to arise from a failure of formylation. A comparison of the capacity of varying folate supplements to mitigate the haematological effects has demonstrated the superior protection afforded by formyl folates (including folinic acid) in comparison with folic acid, tetrahydrofolic acid and 5-methyltetrahydrofolic acid. This protection is difficult to explain on the basis of impaired methionine synthesis and the authors suggest the implied impairment of formylation may be of greater importance than previously recognized (Chanarin et al., 1980).

It has also been demonstrated that, following the return of vitamin B_{12} function, restoration of folate stores require a dietary source of folate (Lumb et al., 1981), but the extent of body stores at the time of nitrous oxide administration is likely to affect the speed of recovery.

Patients exposed to nitrous oxide for 24 h have been shown to develop a temporary megaloblastic haematopoiesis which was averted by the administration of folinic acid 20 mg 12 h and 1 h before the anaesthetic. The authors did not demonstrate bone marrow dysfunction in 30 patients undergoing routine surgical procedures of 1–6 h duration (O'Sullivan et al., 1981). However, Amos and co-workers (1982), in addition to demonstrating a relationship between the degree of abnormality of the dU supression test and the duration of anaesthesia, were able to detect changes following exposure of as little as 1 h in duration.

Although the inhibition of methionine synthase activity is time- and nitrous oxide concentration-dependent in both rat mothers and fetuses, the maternal changes precede those of the fetus (Baden, Serra and Mazze, 1984).

Some investigators have recorded instances where folinic acid has not proven protective (Skacel et al., 1982; Amos et al., 1984).

Perhaps not unexpectedly, treatment of patients with hydroxycobalamin before and immediately after operation did not prevent nitrous oxide-induced bone marrow depression and megaloblastic change (Amess et al., 1978).

The negative results from the present study are in keeping with the work of previous investigators. Whilst it was shown that surgery undertaken in early pregnancy was accompanied by an increased rate of spontaneous abortion, a significant increase in the incidence of congenital abnormalities was not identified in the studies of either Shnider and Webster (1965) or Brodsky and colleagues (1980).

No adverse effects ensued in a case involving 17 general anaesthetics during the course of a pregnancy, including several during the first trimester (Slater, 1970). In a large control-matched series of pregnancies involving surgery it was not possible to identify any influence of either general anaesthetic or surgery on the incidence of congenital abnormalities. However, an increased rate of abortion was noted (Duncan, Pope and Cohen, 1985).

During short procedures such as those involving insertion of Shirodkar suture (20–30 min), particularly where organogenesis is complete, it is unlikely that any significant reduction in fetal thymidine synthesis would occur.

Such protective effects as folinic acid can confer would be of most value in prolonged procedures or during the rapid organogenesis of the first trimester.

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ANAESTHESIA FOR HEART TRANSPLANTATION
A Retrospective Study and Review

K. DEMAS, J. WYNER, F. G. MIHM AND S. SAMUELS

SUMMARY

The anaesthetic records of 261 heart transplant recipients were reviewed. Data collected included demographic characteristics, physical status, results of preoperative cardiac catheterization studies, anaesthetics agents and incidences of complications which may have been related to anaesthetic management. Forty-five patients received a volatile agent (methoxyflurane 31, enflurane 10, halothane 4) and 216 patients were anaesthetized with a high-dose narcotic technique (morphine 122, fentanyl 71, hydromorphone 14, meperidine 9). Hypotension and arrhythmias were correlated with use of volatile and narcotic anaesthetics, respectively. No mortality was associated with anaesthetic management.

Since the first human heart transplantation (Ozinsky, 1967) its success as a treatment has been established for selected patients with end-stage cardiomyopathy. The experience at Stanford has encouraged the establishment of a number of cardiac transplantation centres in the United States and United Kingdom (Oyer et al., 1981; Pennock et al., 1982) particularly since possible alternative therapy for such patients—including the use of a total artificial heart (DeVries et al., 1984) or the insertion of a left-ventricular assist device (Rose et al., 1983)—is still in the experimental phase.

Although several anaesthetic techniques and agents have been used, the literature regarding the anaesthetic management of heart transplantation, for both the initial and any subsequent operation, is sparse (Keats et al., 1969; Paiement et al., 1970; Fernando, Keenan and Boyan, 1978). We review our clinical experience concerning the anaesthetic techniques and agents used at Stanford over the first 15 yr.

PATIENTS AND METHODS

Between January 1968 and May 1982, heart transplantation was undertaken on 261 patients at Stanford University. The charts of all recipients were reviewed and data were extracted concerning demographic characteristics, physical status, results of preoperative cardiac catheterization studies, anaesthetic agents, and the incidences of those complications which may have been related to anaesthetic management. These complications included intraoperative ventricular arrhythmias, systemic arterial hypotension, prolonged postoperative requirement for mechanical ventilation, renal failure and the development of either global neurological dysfunction or focal neurological deficits. Hypotension during anaesthesia was defined as a systolic arterial pressure of less than 90 mm Hg, a diastolic arterial pressure of less than 50 mm Hg, or a mean arterial pressure of less than 60 mm Hg determined on more than two readings, 5 min apart. Postoperative mechanical ventilation was considered prolonged when this was required for more than 24 h after transplantation. Ventricular arrhythmias were defined as significant only if these required specific therapeutic intervention (cardioversion, drugs). Renal failure was defined as significant only if haemodialysis was required. Chi square analysis was used to relate the incidences of these complications to the anaesthetic technique used and was considered statistically significant if the P value was < 0.05. The incidence and causes of death within 1 week after transplantation were also reviewed. Similar data were collected pertaining to all subsequent anaesthetics administered to cardiac transplant

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KATHRYN DEMAS, M.D.; JANET WYNER, M.B., CH.B; FREDERICK G. MIHM, M.D.; STANLEY SAMUELS, M.B., CH.B.; Department of Anesthesia S278, Stanford University School of Medicine, Stanford, CA 94305, U.S.A.
Correspondence to J. W.

recipients. A total of 397 anaesthesia records were reviewed which included cardiac transplantation (237), repeat transplantation (24) and anaesthesia for a subsequent surgical procedure (136).

RESULTS

Demographic data

Recipients ranged in age from 12 to 58 yr. The primary diagnoses of recipients were: ischaemic cardiomyopathy, 45%; idiopathic cardiomyopathy, 46%; valvular heart disease, 4.7%; congenital heart disease, 1.7%; post-traumatic aneurysm, and primary cardiac tumour, 0.4%. Twenty-four patients underwent a second transplantation, the reasons for which included atherosclerosis or rejection of the donor heart.

Preoperative physical status

All patients were classified as New York Heart Association Class IV or V. Physical signs of congestive heart failure were present in the majority of cardiac transplant recipients on the day of surgery (table I). Twelve percent required pharmacological inotropic support before surgery and a further 2% required mechanical circulatory support with intra-aortic balloon counterpulsation (table I). Renal dysfunction, as reflected by increases in BUN and creatinine concentrations, and liver dysfunction, as defined by a non-iatrogenic increase in prothrombin time, were present before operation in 41% and 52% of patients, respectively. Preoperative ventricular arrhythmias were reported in 12% of patients, and were most common in patients suffering from idiopathic cardiomyopathy.

TABLE I. *Evidence of ventricular failure in cardiac transplantation recipients on day of operation*

Evidence	Incidence
Symptoms	
Orthopnoea	42%
Dyspnoea	42%
Peripheral oedema	27%
Physical signs	
Rales	44%
S3 gallop	67%
Jugular venous distension	47%
Hypotension	28%
Oliguria	3%
Chest radiograph	
Pleural effusion	8%
Pulmonary oedema	7%
Circulatory support	
Inotropic drugs	12%
Intra-aortic balloon	2%

TABLE II. *Results of preoperative cardiac catheterization studies in cardiac transplant recipients. RAP = right atrial pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; LV = left ventricular (end-diastolic) pressure; PA = pulmonary artery*

	Mean	SD
RAP mean (mm Hg)	12	8
PAP systolic (mm Hg)	50	17
PAP diastolic (mm Hg)	27	10
PCWP mean (mm Hg)	27	9
LV end-diastolic (mm Hg)	27	2
Cardiac output (litre min^{-1})	3.3	2.5
Cardiac index (litre min^{-1} m^2 BSA)	1.8	1.3
PA O_2 saturation (%)	48	16

Preoperative cardiac catheterization data

Most often, the cardiac catheterization data demonstrated marked left ventricular dysfunction as indicated by increases in left ventricular end-diastolic pressures and pulmonary capillary wedge pressures, and low cardiac indices (table II). Since the selection criteria eliminated those patients with severe pulmonary hypertension (pulmonary vascular resistance greater than 6 Wood-units), the close relationship between the pulmonary diastolic and capillary wedge pressures and the absence of marked increases in right-sided pressures were expected findings.

Anaesthetic agents

After aseptic placement of intravascular catheters and attachment to appropriate monitors, anaesthesia was induced with either an inhalation or an i.v. technique. During the early period of cardiac transplantation at Stanford, the preferred anaesthetic agent was methoxyflurane in oxygen. However, with the subsequent documentation of this agent's nephrotoxicity, its use was abandoned (Mazze, Shue and Jackson, 1971). After the introduction of the high-dose narcotic technique for cardiac anaesthesia (Lowenstein, Hallowell and Levine, 1969; Stanley and Webster, 1978), this method soon became popular for the anaesthetic management of cardiac transplantation. Of the patients studied, 45 received a volatile agent as the primary anaesthetic drug and 216 were anaesthetized with a high-dose narcotic–oxygen technique (table III). There has also been a trend towards the use of fentanyl or hydromor-

TABLE III. *Anaesthetic agents*

Agent	Patients
Volatile	
Methoxyflurane	31
Enflurane	10
Halothane	4
Narcotic	
Morphine 1.5–2 mg kg^{-1}	122
Fentanyl 25–75 μg kg^{-1}	71
Hydromorphone 0.2–0.5 mg kg^{-1}	14
Pethidine 10 mg kg^{-1}	9
Benzodiazepine	
Diazepam 0.2–0.3 mg kg^{-1}	85

TABLE V. *Surgical procedures performed after cardiac transplantation. *Usually abcess drainage. †Vascular access, vocal cord nodules, condylomata, skin grafts, etc.*

Emergency exploration for mediastinal bleeding	13
Complications caused by infection*	
Laparotomy	7
Craniotomy	7
Mediastinotomy/thoractomy	19
Extremity abscess drainage	7
Bronchoscopy	2
Vitrectomy	2
Scleral buckle	1
Complications caused by steroid treatment	
Total hip arthroplasty or pinning	9
Laparotomy for perforated viscus	13
Cataract excision	1
Vascular surgery	
Aortic	5
Peripheral	8
Amputations	7
Cardioversion	6
Elective cholecystectomy	3
Miscellaneous†	26

phone rather than morphine or pethidine over the past 5 years. Diazepam 0.2–0.3 mg kg^{-1} was used to supplement narcotic anaesthesia in 85 patients.

Complications

The major complications encountered are tabulated in table IV. The incidence of hypotension was significantly lower when narcotic agents were used, while serious ventricular arrhythmias occurred more often with this technique. Seven patients who had not required haemodialysis before surgery required dialysis after transplantation. All of these patients had some preoperative renal dysfunction. The incidences of both prolonged mechanical ventilation and new onset renal failure were low (< 3%) and not significantly different between the patients receiving different anaesthetic techniques.

Gross neurological deficits after transplantation were uncommon, occurring in only six patients. Of the six patients, two were in preoperative cardiogenic shock when a donor became available, two suffered early postoperative cardiac arrest (within 72 h), and three suffered from postoperative septicaemia with renal and hepatic dysfunction. Five other patients had focal neurological deficits. None of these neurological complications could be ascribed to the anaesthetic agent(s) or technique.

Five deaths occurred within 7 days of transplantation, of which three occurred during surgery. One patient could not be weaned from cardiopulmonary bypass because of right heart failure associated with pulmonary embolization and pulmonary hypertension, and in the other two death was caused by uncontrollable haemorrhage. Two more deaths occurred within 72 h of surgery: one was associated with right heart failure secondary to pulmonary hypertension (as the donor heart was too small to work against the high pulmonary vascular resistance) while, in the other, hyperacute rejection of the donor heart occurred. Mortality rate and anaesthetic technique were not correlated.

TABLE IV. *Incidence of complications in anaesthesia for cardiac transplantation. *P values obtained from Chi square analysis comparing the incidences of each complication between volatile and narcotic groups*

	Anaesthetic		
Complication	Volatile (n = 45)	Narcotic (n = 186)	P*
Hypotension	51%	21%	< 0.05
Mechanical ventilation > 24 h	2%	3%	ns
Ventricular arrhythmia	9%	21%	< 0.05
Renal failure	2%	3%	ns

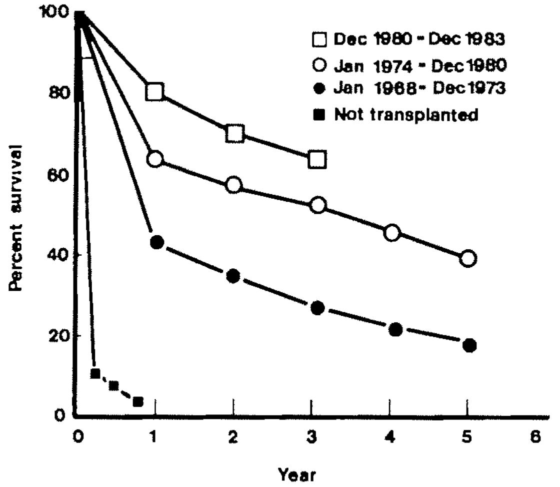

FIG. 1. Actuarial survival rates of patients undergoing cardiac transplantation between January 1968 and December 1983. Poor survival rate of patients chosen as potential recipients but not transplanted is indicated.

Anaesthesia for surgery on post-cardiac transplant patients

Subsequently, 80 recipients underwent 136 anaesthetics for a variety of surgical procedures, both emergency (55 %) and elective (45 %) (table V). These procedures were performed from 2 h to 6 yr after transplantation. General anaesthesia was the preferred technique and only 4.4% of patients received a regional anaesthetic technique. The preferred agents for general anaesthesia were: nitrous oxide–oxygen and narcotic (35 %), narcotic–oxygen only (18 %), and inhalation agent (23 %) and other i.v. agents (28 %) including thiopentone (10 %) and ketamine (8 %).

Endotracheal intubation was performed in 102 patients. Extubation in the operating room was accomplished in 53 %, and extubation within 24 h was achieved in a further 25 %. Complications included hypotension on induction (10 %), and ventricular arrhythmias (< 1 %) which were not significantly associated with any anaesthetic technique. One intraoperative death occurred in a patient undergoing drainage of a lung abscess. In that instance, a double-lumen endobronchial tube had been placed, but when the patient was turned to a lateral thoracotomy position, severe hypoxia occurred which led to bradycardia, and this progressed to asystole.

DISCUSSION

There has been a substantial improvement in survival over the past 6 years, resulting from refinement in patient selection, improved postoperative care and the introduction of cyclosporin. Approximately 80 % of patients currently undergoing transplantation may be expected to survive 1 year, and between 60 and 65 % of patients survive for 3 years (fig. 1). Patients accepted as candidates for transplantation for whom an acceptable donor heart cannot be found quickly have much poorer survival rates. Only 10 % of accepted candidates who have not undergone transplantation within 3 months of selection survive to undergo surgery (Oyer et al., 1981; Pennock et al., 1982).

Anaesthesia for cardiac transplantation can be successfully performed with a number of anaesthetic agents. Review of major anaesthetic-related complications revealed no deaths or permanent injury associated with anaesthetist error or choice of anaesthetic agent. The choice of anaesthetic agent to be used for this procedure, as for any operation requiring general anaesthesia, should be based on the risk/benefit ratio for that particular agent.

Volatile agents have the potential to cause profound myocardial depression and vasodilatation. Narcotics produce less myocardial depression and vasodilatation, but will be eliminated more slowly than inhalation agents, especially in patients with impaired liver or renal function. Therefore, in this particular patient population, narcotics would be expected to provide better haemodynamic stability than inhalation agents while, possibly, resulting in a requirement for prolonged ventilatory support in the postoperative period.

The incidence of precardiopulmonary bypass hypotension was significantly greater in the group of patients anaesthetized with volatile anaesthetics than in those patients who received narcotics. Several prospective studies in patients undergoing coronary artery bypass and valvular surgery have demonstrated the safety of inhalation anaesthesia in patients with normal ventricular function, although more depression in myocardial contractility occurs with halothane than with narcotics (morphine) (Conahan et al., 1973; Moffitt et al., 1982). The severity of the pre-existing left ventricular dysfunction in our patients may have enhanced the known depressant effects of the volatile anaesthetics. However, there may be instances when low concentrations of volatile agents can be used safely to supplement narcotic anaesthesia in transplant recipients with less severely impaired ventricular function.

Prolonged postoperative mechanical ventilation may be hazardous because of the predilection for pulmonary infection; bacterial and opportunistic infections remain a major cause of mortality in this immunosuppressed population. We found no difference in the need for prolonged postoperative ventilatory support between the patients receiving narcotics and those receiving inhalation anaesthetics. This finding supports the choice of narcotic anaesthesia for heart transplantation. The higher incidence of ventricular arrhythmias in patients receiving narcotic anaesthetics may reflect less profound depression of sympathoadrenal responsiveness. However, arrhythmias were treated readily by either cardioversion or antiarrhythmic drugs and thus should not contraindicate the use of a narcotic technique.

Management of the cardiac donor is crucial to the success of heart transplantation, as the anaesthetist must protect the donor heart from injury until it is harvested. All donors have irreversible brain injury and many have been treated with diuretics in an attempt to decrease intracranial pressure. In addition, diabetes insipidus is common. Therefore, hypovolaemia must be treated vigorously with fluid replacement as well as with appropriate doses of vasopressin in order to minimize the need to support the arterial pressure with vasoactive drugs. If other organs such as kidneys, liver and eyes are to be harvested for transplantation, the anaesthetist should be familiar with the special needs of the other surgical teams.

Cardiac transplantation is performed when a donor heart becomes available. Consequently, surgery is undertaken as an emergency and most patients will have full stomachs. Cyclosporin A (Pennock et al., 1981), a fungal metabolite which has been shown to suppress rejection of organ grafts, is given to all patients. Approximately 20 ml (10–18 mg kg^{-1}) of this drug is given orally shortly before the induction of the anaesthetic. Therefore, in all patients the volume of the stomach contents is assumed to be greater than 25–50 ml. Premedication is usually withheld until the patient arrives in the operating suite.

Many patients undergoing cardiac transplantation will have abnormal coagulation indices, either secondary to passive congestion of the liver or because they have been treated with anticoagulant drugs to prevent embolic events. All patients are immunosuppressed; therefore, precautions to avoid contamination of drugs and the surgical field should be observed. Our practice includes placing intravascular catheters using aseptic techniques. All airway equipment, including the tubing of the circle system, is sterile and handled with sterile gloves when transplant recipients are anaesthetized. Bacterial filters are used routinely in both limbs of the circle system. Standard monitoring includes: the electrocardiogram, arterial and central venous pressures, bladder and nasopharyngeal temperatures, oesophageal stethoscope and urinary volumes. Central venous catheters can be placed via several routes, but we prefer the left internal jugular vein, which leaves the right internal jugular vein available for future cardiac biopsies. Arterial cannulae are placed percutaneously in a radial artery avoiding a cutdown because of the risk of infection. Pulmonary artery catheters have not been used because they would have to be removed from the surgical field when the donor heart is excised and, if placed after transplantation, would cross a surgical anastomosis.

Our current anaesthetic regimen for cardiac transplantation consists of fentanyl 30–50 μg kg^{-1} or sufentanil 15–20 μg kg^{-1}, diazepam 0.1–0.3 mg kg^{-1}, and ventilation with 100% oxygen. After pre-oxygenation, anaesthesia is induced while maintaining cricoid pressure. Nitrous oxide is seldom used because the recipient heart, donor heart, and great vessels are opened during the surgical procedure, and avoiding the use of nitrous oxide minimizes the risk of enlarging an inadvertent air embolus. Pancuronium 0.1 mg kg^{-1}, is the most commonly used neuromuscular blocking agent; however, other blockers have been found equally useful. Metocurine 0.3 mg kg^{-1} or vecuronium 0.1 mg kg^{-1}, is sometimes used. Recently, the combination of pancuronium and metocurine, each in one-half of the usual intubating dose, has become popular because of speed of onset and minimal cardiovascular effects (Lebowitz et al., 1980).

In our institution, cardiopulmonary bypass for cardiac transplantation utilizes a low-pressure low-flow technique which is used routinely for other forms of cardiac surgery. Flow rates are approximately 40 ml kg^{-1} min^{-1} with an average flow rate of 3.0/3.5 litre min^{-1}, adjusted to keep mean arterial pressure 30–60 mm Hg. The patient is cooled 28–30 °C (rectal temperature). No attempt is made to terminate cardiopulmonary bypass until the patient has been warmed to a nasopharyngeal temperature greater than 34 °C, and until the electrocardiogram has returned to its normal configuration. It should be remembered that the donor heart is denervated and remains denervated. Junctional rhythms secondary to acute denervation and to surgical trauma are common, especially in the immediate post-transplantation period. The patient's cardiac output will be largely rate-dependent in the first few days after transplantation and, therefore, before cardiopulmonary bypass is terminated, an isoprenaline infusion is started and titrated to maintain a heart rate of 100–120 beat min^{-1}. Infusion of pressor agents, usually dopamine, may be required if the donor heart appears to be contracting poorly. Sodium nitroprusside is used after cardiopulmonary bypass, to decrease afterload and to provide controlled venodilatation, which permits intravascular volume expansion in hypothermic patients. After cardiopulmonary bypass has been terminated successfully, methylprednisolone 500 mg is administered i.v. The effect of the heparin is reversed routinely with protamine and, because preoperative coagulation abnormalities are aggravated by cardiopulmonary bypass, most patients require the replacement of coagulation factors with fresh frozen plasma and platelets.

The responses of the cardiac transplant recipient to pharmacological and volume manipulations are predictable as the transplanted heart remains free of autonomic reinnervation (Cannon, Graham and Harrison, 1973; Cannon et al., 1975). The innervated atrium of the recipient is haemodynamically insignificant while the donor atrium, which is denervated, is responsible for the electrophysiological responses of the transplanted heart (Goodman et al., 1976). To date, no evidence of reinnervation of the transplanted human heart has been demonstrated for as long as 44 days after surgery. However, long-term cyclosporin-treated patients have not been studied. In cyclosporin-treated monkeys, reinnervation of both the heart and lungs after transplantation has been demonstrated (Popovich et al., 1982, 1983). The denervated heart retains its intrinsic control mechanisms, which include: a normal Frank–Starling effect demonstrated with volume loading and in response to exercise (Pope et al., 1980); normal impulse formation and conductivity (Cannon, Graham and Harrison, 1973; Cannon et al., 1975; Goodman et al., 1976); and intact alpha- and beta-adrenoceptors without evidence of denervation hypersensitivity (Cannon et al., 1975). The coronary vasculature retains its response to changes in metabolic demand, but loses its basal alpha-adrenergic tone and resting coronary blood flow is, thereby, increased (Orlich et al., 1978). Coronary arteries remain responsive to adrenergic drugs.

Patients with denervated hearts lack the ability to respond acutely to hypovolaemia or hypotension with reflex tachycardia. Accordingly, increases in cardiac output are dependent upon increases in venous return until the circulating catecholamine concentrations increase sufficiently to increase heart rate and contractility. The anaesthetist managing patients who are transplant recipients should remember, therefore, that intravascular volume depletion may be poorly tolerated by these patients, particularly if associated with anaesthetic agents which suppress the sympatho-adrenal system. Any technique, especially major conduction anaesthesia, which is associated with hypotension secondary to vasodilatation should be used with caution. Preload manipulation will be important, and a directly-acting chronotropic drug such as isoprenaline and a direct vasoconstrictor such as phenylephrine should be available. Agents such as pancuronium, atropine and anticholinesterases will have no effect on the denervated heart. Only drugs acting on the heart directly, without involvement of the autonomic nervous system, can be expected to affect the donor heart. Drugs such as digoxin and quinidine which act through mixed autonomically mediated and direct mechanisms will produce only their direct effects (Goodman et al., 1975; Mason et al., 1977). Atrial, junctional and ventricular arrhythmias are common in the denervated heart, especially in the first 6 months after transplantation, with the incidence increasing during episodes of rejection (Schroeder et al., 1974; Romhilt et al., 1982). These rhythms respond to the treatment of rejection and, if haemodynamically significant, can be treated with electrical cardioversion or with antiarrhythmic drugs which act directly on the conducting system. Sinus tachycardia is not considered abnormal in transplant recipients. Free from resting vagal tone, the transplanted heart has a resting rate of 90–120 beat min^{-1}.

Experience with subsequent anaesthetics for both emergency and elective procedures in cardiac transplant recipients has demonstrated that a variety of techniques can be used safely (Kanter and Samuels, 1977). Functional impairment of the transplanted heart is usually not present unless the patient is in acute rejection. Transplant recipients are compromised hosts on long-term immunosuppressive therapy and several considerations are pertinent. Chronic steroid treatment may result in an abnormal stress response; therefore, most patients receive steroids before and during the operation. Most importantly, strict aseptic precautions must be observed to avoid infection. As with the primary procedure, intravascular monitoring, the administration of drugs and airway manipulations should be performed as aseptically as possible. Unless invasive intravascular monitoring will yield information of crucial importance, as in the acutely rejecting recipient, it should be avoided. Postoperative mechanical ventilation should also be avoided, when possible, to avoid the risk of pulmonary infection.

The experience with anaesthesia for cardiac transplantation at Stanford University Medical Center has demonstrated that both narcotic anaesthetic techniques and inhalation techniques (table IV) may cause complications. The anaesthetist must remember that the patient undergoing the procedure is one with severely impaired ventricular function and often with reversible hepatic or renal dysfunction, or both, secondary to a low cardiac output state. The consequences of autonomic denervation of the heart should be remembered in the post-cardiopulmonary bypass period, and during any subsequent anaesthetic in transplant recipients. Since infection remains a major cause of morbidity and mortality in this immunosuppressed population, aseptic techniques must be used.

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EFFECT OF HALOTHANE ON CARDIOVASCULAR AND PLASMA CATECHOLAMINE RESPONSES TO TRACHEAL INTUBATION

D. A. B. TURNER, A. J. SHRIBMAN, G. SMITH AND K. J. ACHOLA

SUMMARY

The catecholamine and cardiovascular responses to intubation were investigated during halothane anaesthesia. Thirty patients were allocated randomly to two groups. Following induction of anaesthesia and muscle relaxation, group 1 was ventilated with 70% nitrous oxide in oxygen before intubation; group 2 received 1% halothane in addition. After intubation, both groups received 0.5% halothane. Arterial pressure and heart rate, and plasma noradrenaline and adrenaline concentrations were measured throughout the induction sequence. In group 1 intubation was associated with increases (from pre-induction values) in systolic arterial pressure of 13% and diastolic arterial pressure of 35%, although the plasma concentrations of noradrenaline did not alter significantly. In group 2, although there was a pressor response to intubation, no overall change in systolic arterial pressure and only a 13% increase in diastolic arterial pressue occurred when compared with pre-induction values. This response was associated with a 78% increase in the noradrenaline concentration; the adrenaline concentration did not alter significantly.

The cardiovascular responses to laryngoscopy and tracheal intubation have been investigated for more than 30 years (King et al., 1951; Prys-Roberts et al., 1971; Stoelting, 1977), and it is generally agreed that the pressor response to intubation may be harmful (Fox et al., 1977). Although a large variety of agents and techniques has been utilized in attempts to attenuate this response—with varying degrees of success (Siedlecki, 1975; Fox et al., 1977; Derbyshire and Smith, 1984)—no single technique has become universally successful or acceptable.

Many anaesthetists use an induction sequence of thiopentone, neuromuscular blockade and a few minutes manual ventilation of the patient's lungs with oxygen and nitrous oxide (with or without the addition of a volatile agent) before laryngoscopy. This technique is accompanied frequently by a significant pressor response to tracheal intubation (Ward et al., 1965; Kautto and Saarnivaara, 1983; Bedford and Marshall, 1984). However, it is known that, if the depth of anaesthesia is increased, the pressor response to intubation is reduced although, under these circumstances, the risk of cardiovascular depression before the onset of surgery is increased.

In recent years, the development of accurate techniques for the measurement of the plasma concentrations of the catecholamines has invited attempts to correlate the blood concentrations of these hormones with the changes in cardiovascular variables observed during the induction of anaesthesia. A radioenzymatic method, first described by Engelman, Portnoy and Lovenberg (1968), and a high pressure liquid chromatographic (HPLC) technique (Hallman et al., 1978) have been used, and significant increases in plasma noradrenaline concentration have been correlated with significant pressor responses to intubation (Russell et al., 1981; Derbyshire et al., 1983).

Recently, it has been suggested that the induction of anaesthesia with halothane produces

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D. A. B. TURNER, M.B., CH.B., F.F.A.R.C.S.; A. J. SHRIBMAN*, M.B., B.S., F.F.A.R.C.S.; G. SMITH, B.SC., M.D., F.F.A.R.C.S.; K. J. ACHOLA, M.SC.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW.

*Present Address: Department of Anesthesia, Medical College of Virginia, Richmond, Virginia, U.S.A.

Correspondence to D.A.B.T.

an increase in plasma noradrenaline concentration (Joyce et al., 1982), although the use of halothane at induction is a suggested technique for attenuating the pressor response to intubation. The present study was designed to investigate more fully the catecholamine and cardiovascular responses induced by laryngoscopy and tracheal intubation during halothane anaesthesia.

PATIENTS AND METHODS

Thirty patients (ASA Grades I or II) undergoing elective surgery under anaesthesia requiring tracheal intubation gave their informed consent for the study which was approved by the District Ethical Committee. The patients were allocated randomly to two groups.

Premedication comprised papaveretum 0.3 mg kg^{-1} and hyoscine 0.1 mg/20 kg given i.m. 1 h before operation. In the anaesthetic room a 23-gauge cannula was placed in the back of the hand and a 16-gauge cannula in a vein in the ipsilateral antecubital fossa after local intradermal injection of 0.5% plain lignocaine. Arterial pressure was measured (Dinamap) on the contralateral arm, and ECG electrodes attached to record standard limb lead II. After a stabilization period of 5 min, control readings of arterial pressure and heart rate (from the ECG) were noted and 10 ml of blood drawn from the cannula in the antecubital fossa for measurement of plasma adrenaline and noradrenaline concentrations.

Induction of anaesthesia was accomplished with a dose of thiopentone sufficient to induce sleep (3–4 mg kg^{-1}), and was followed by vecuronium 0.1 mg kg^{-1}. The patient's lungs were ventilated for 3 min via a mask attached to a Bain breathing system receiving a fresh gas flow of 90 ml kg^{-1}. Patients in group 1 received 70% nitrous oxide in oxygen whilst those in group 2 received 1% halothane and 70% nitrous oxide in oxygen.

Ventilation and fresh gas flows were adjusted to maintain the end-expired carbon dioxide at a concentration of 5–5.5%, as measured by a Datex capnograph using a sampling catheter placed under the mask. The accuracy of the halothane vaporizer was verified before the study using an MGA 200 mass spectrometer.

Arterial pressure and heart rate were recorded at 1-min intervals, and at 3 min after induction the patient's trachea was intubated. For the following 7 min, patients in both groups received 0.5% halothane and 70% nitrous oxide in oxygen. Further venous samples were taken at 2, 4 and 8 min following induction (that is at 1 min before, and 1 and 5 min after tracheal intubation).

The 10-ml blood samples were collected into pre-cooled, heparinized "Vacutainer" tubes and stored immediately in ice. Samples were centrifuged as soon as possible. The separated plasma was stored at −70 °C until analysis was performed for noradrenaline and adrenaline concentrations using an HPLC technique described by Hallman and colleagues (1978) as adapted in our laboratory (Fell, Achola and Smith, 1982; Derbyshire et al., 1983).

Data were analysed using paired and unpaired Student's t tests as appropriate.

RESULTS

The two groups were similar in respect of age, weight and sex (table I).

Mean heart rates before the induction of anaesthesia were similar in each group and there were no significant changes during the first 3 min after induction (fig. 1). However, at 1 min after tracheal intubation there were significant increases ($P < 0.001$) of approximately 25% in heart rate in both groups. These decreased gradually towards their pre-induction values over the subsequent 6 min.

Mean systolic arterial pressures before induction were similar in both groups (fig. 2). Following induction, systolic arterial pressures had decreased significantly by approximately 10% in both groups at 1 min. After 3 min of ventilation with 1% halothane and 70% nitrous oxide in oxygen the systolic arterial pressure in group 2 was significantly lower than that in group 1 ($P < 0.05$). The mean diastolic arterial pressure before induction was significantly higher in group 2 ($P < 0.01$). After induction (at 1 min) the diastolic arterial pressure in group 1 had not altered significantly. In group 2, however, the diastolic arterial pressure had decreased significantly (by approximately 15% ($P < 0.001$)) to a

TABLE I. *Details of patients (mean (SEM))*

	Age (yr)	Weight (kg)	Sex
Group 1 0% Halothane ($n = 15$)	46.3 (4.1)	67.2 (2.4)	7M 8F
Group 2 1% Halothane ($n = 15$)	53.4 (4.1)	71.2 (3.0)	5M 10F

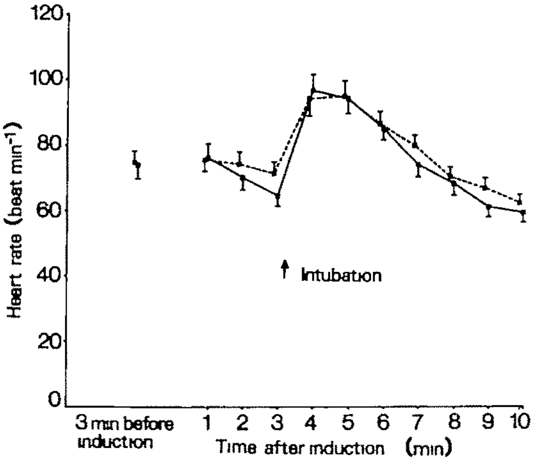

FIG. 1. Heart rates in both groups before induction and for the 10-min period after induction (mean (SEM)). □- - -□ = Group 1 (0% halothane; $n = 15$); ■——■ = group 2 (1% halothane; $n = 15$).

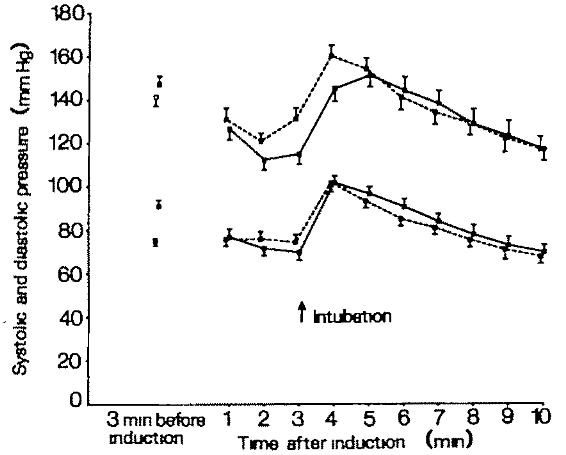

FIG. 2. Systolic and diastolic arterial pressures in both groups before induction and for the 10-min period after induction (mean (SEM)). □- - -□ = Group 1 (0% halothane; $n = 15$); ■——■ = group 2 (1% halothane; $n = 15$).

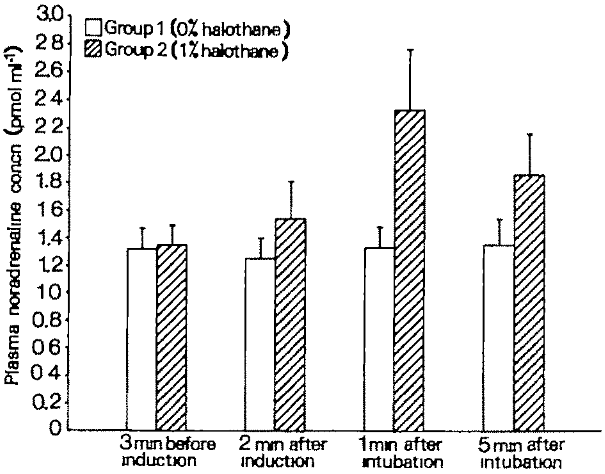

FIG. 3. Plasma noradrenaline concentrations in both groups at each stage of the study (mean (SEM)). Group 1: $n = 13$; group 2: $n = 12$.

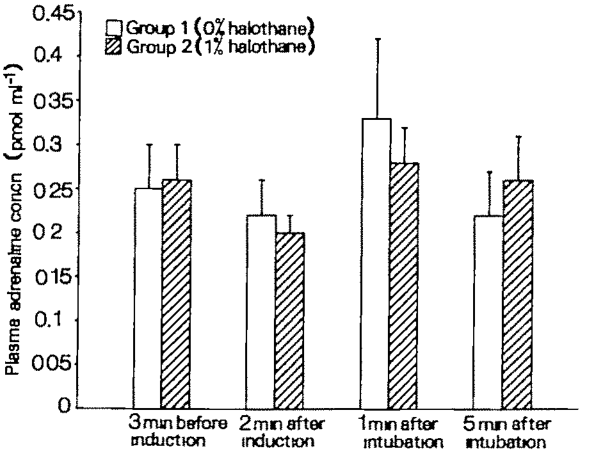

FIG. 4. Plasma adrenaline concentrations in both groups at each stage of the study (mean (SEM)). Group 1: $n = 13$; group 2: $n = 12$.

value similar to group 1. At 3 min after induction the diastolic arterial pressures in the two groups were similar.

In both groups tracheal intubation was associated with significant increases in systolic and diastolic arterial pressures and these were maximal at 1 min after intubation ($P < 0.001$). The increase (26%) in systolic arterial pressure in group 2 was such that, after intubation, it did not differ significantly from the pre-induction value. In group 1 the systolic arterial pressure increased by approximately 22% and was significantly higher than its pre-induction value ($P < 0.001$). After a subsequent 1 min, the systolic arterial pressures were similar in both groups and within 5 min they were similar to the pre-intubation values. Diastolic arterial pressures in both groups had increased by approximately 40% 1 min after intubation. However, when compared with the pre-induction values the increases were 35% for group 1 and 13% for group 2.

Mean pre-induction plasma noradrenaline concentrations were similar in both groups (fig. 3). In group 1, the concentrations remained unchanged

TABLE II. *Changes in plasma noradrenaline and adrenaline concentrations expressed as mean (SEM) percentage change from control values. Value significantly different from group 1:* *$P < 0.05$; **$P < 0.02$

Time after induction (min)	Noradrenaline Group 1 ($n = 13$)	Noradrenaline Group 2 ($n = 12$)	Adrenaline Group 1 ($n = 13$)	Adrenaline Group 2 ($n = 12$)
2	+0.2 (9.0)	+21.8 (20.1)	−2.2 (13.0)	−13.5 (14.1)
4	+10.3 (14.2)	+77.7 (24.4)**	+18.6 (16.0)	+34.6 (23.7)
8	+7.5 (9.5)	+44.2 (19.6)*	−3.0 (13.0)	+9.4 (19.1)

throughout the study. In group 2, the mean plasma noradrenaline concentration was significantly greater at 1 min following intubation than at 3 min before induction ($P < 0.02$), and was significantly greater than the corresponding value in group 1 ($P < 0.05$). The mean pre-induction plasma adrenaline concentrations were similar in both groups and, although the values decreased after induction and increased after intubation, the changes were not significant (fig. 4).

When the plasma catecholamine data are expressed as percentage change from control values, it may be seen that, 1 min after intubation (4 min after induction), there was an increase in plasma noradrenaline concentration in group 2 of almost 78%, which was significantly greater ($P < 0.02$) than the 10% increase in group 1 (table II). The increase in plasma noradrenaline concentration in group 2 was still evident at 5 min after intubation. There was a mean percentage increase in plasma adrenaline concentration after intubation of nearly 20% in group 1 and of more than 30% in group 2, although these increases were not significant.

DISCUSSION

This study was designed to examine two questions. First, does the addition of 1% halothane to the inspired gas mixture for 3 min after the induction of anaesthesia significantly influence the cardiovascular responses to subsequent laryngoscopy and intubation? Second, is the administration of halothane before tracheal intubation associated with alterations in catecholamine concentrations.

For the purposes of this study, blood was sampled from the antecubital fossa. Derbyshire and colleagues (1983) have shown that the noradrenaline and adrenaline concentrations in blood from this site are similar to those in arterial and mixed venous blood. With regard to single measurements of catecholamine concentrations, Derbyshire and Smith (1984), in a recent review, acknowledged that they "represent only a brief glimpse of the overall extent of sympathoadrenal activity", but concluded that they "augment haemodynamic measurements as indirect indices".

The results demonstrated that the addition of halothane had no demonstrable effect on the increase in heart rate associated with intubation. In addition, a pressor response to intubation was observed in both groups, but because halothane had decreased arterial pressure before intubation in group 2, these patients did not become hypertensive after intubation. Kautto and Saarnivaara (1983), however, found that the administration of either 2% halothane or 3% enflurane with 70% nitrous oxide in oxygen for 2 min did significantly attenuate the pressor response.

Bedford and Marshall (1984) compared four different anaesthetic techniques and concluded that, although 0.4% halothane prevented significant increases in arterial pressure following intubation, it was not the ideal agent since it did not prevent an increase in heart rate or pulmonary capillary wedge pressure. They concluded that both 0.7% enflurane and a combination of fentanyl 5 $\mu g\ kg^{-1}$ and droperidol 250 $\mu g\ k^{-1}$ were more suitable alternatives.

The relationship between inspired halothane concentrations and plasma catecholamine concentrations has been examined in animal preparations. Naito and Gillis (1973) found that halothane reduced the removal of noradrenaline by isolated, perfused rabbit lungs and Joyce and colleagues (1982) observed that halothane initially increased the release of noradrenaline from isolated, perfused cat spleens. In contrast, Roizen and colleagues (1974) noted that halothane depressed arterial catecholamine concentrations in the rat and concluded that this resulted from inhibition of catecholamine release from sympathetic nerves and the adrenal medulla. In addition, Perry, Van Dyke and Theye (1974) found that halothane had no significant influence on circulating plasma concentrations of noradrenaline or adrenaline in the dog.

The relationship between plasma catecholamine concentrations and halothane is also unclear in man and this has been discussed in the review by Derbyshire and Smith (1984). Whilst Joyce and colleagues (1982) found that halothane increased plasma noradrenaline concentrations during the induction of anaesthesia, they were unable to correlate arterial pressure with noradrenaline concentration and concluded that the increase in noradrenaline concentration was not solely a response to the hypotension induced by the halothane.

In the present study, there was a significant decrease in arterial pressure in both groups after induction. In the group given halothane, this decrease was sustained until tracheal intubation (fig. 2), and during the pre-intubation period there was no change in plasma noradrenaline concentration. This suggests that halothane-induced hypotension was not the cause of the increase in noradrenaline concentration reported elsewhere during halothane anaesthesia.

Russell and colleagues (1981) have demonstrated a correlation between the increases in arterial pressure and the plasma noradrenaline concentration following intubation in patients paralysed with pancuronium. In addition, Derbyshire and colleagues (1983) found a correlation in patients given suxamethonium, but not pancuronium. The present study was unable to demonstrate any correlation between the changes in systolic or diastolic arterial pressures, pulse pressure or heart rate with changes in the concentrations of either noradrenaline or adrenaline.

The present study has shown that patients who did not receive halothane exhibited significant increases in arterial pressure in response to intubation, to values significantly greater than those observed before induction. However, the concentration of noradrenaline increased by only a small, non-significant amount. In contrast, those who received halothane also exhibited a significant increase in arterial pressure after intubation, but only to its pre-induction value and yet, in this group, the noradrenaline concentration increased significantly. Halothane, therefore, appeared to be associated with a greater release of noradrenaline in response to intubation.

It is suggested that any pressor effect which might accompany the increases in noradrenaline concentration was offset by the reduction in myocardial contractility induced by halothane. Before intubation, 1 % halothane administered for 3 min was not associated with a change in noradrenaline concentrations. After intubation all patients received 0.5 % halothane for 7 min and those who were given halothane for the first time (group 1) also showed no change in noradrenaline concentration. Thus we were unable to demonstrate an effect of halothane in the absence of intubation.

In their study, Joyce and colleagues (1982) found that 1.5 % halothane in oxygen, given to patients breathing spontaneously through a mask over a 15-min period, was associated with almost a doubling of the mean plasma noradrenaline concentration. They discussed in detail possible mechanisms and concluded that either direct stimulation or a greater depression of inhibitory synapses could be leading to an increased release of noradrenaline from sympathetic nerve endings, rather than a change in reuptake or metabolism at the nerve ending. Our study demonstrated an increase in noradrenaline concentration only after intubation, presumably because the stimulation from the laryngoscopy augmented any effect of halothane, on noradrenaline release from sympathetic nerve endings, which was not evident in the unstimulated state.

It may seem surprising that we have not observed an increase in catecholamine concentrations following tracheal intubation in the group not receiving halothane, in view of the previously published study from this Department which demonstrated a significant pressor and catecholamine response (Derbyshire et al., 1983). However, in the present study the pre-induction concentrations of both noradrenaline and adrenaline were approximately one-half those in the previous study and it may be that the premedication with papaveretum and hyoscine rather than diazepam and droperidol was influencing both the basal concentrations of catecholamines and their response. Other aspects of methodology also differed between the two studies.

In conclusion, the results of this study would support the view expressed by Joyce and colleagues (1982) that halothane is associated with an increase in the plasma concentration of noradrenaline. Although we demonstrated this effect only following the stimulation of intubation, Joyce and colleagues observed the effect in the unstimulated state in conditions different from these pertaining in the present study. We have also demonstrated that 1% halothane given for 3 min before intubation does not prevent the pressor response, but will prevent hypertension in response to endotracheal intubation in healthy adults. This study was performed in patients in ASA grades I or II; patients with significant cardiovascular disease could develop more profound hypotension before intubation if this technique is used.

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IBUPROFEN IN THE MANAGEMENT OF POSTOPERATIVE PAIN

H. OWEN, R. J. GLAVIN AND N. A. SHAW

SUMMARY

The effect of the regular administration of ibuprofen on pain following abdominal surgery was investigated in a double-blind placebo-controlled study. The analgesic action of ibuprofen was measured by a reduction in the amount of morphine self-administered from an On-Demand Analgesic Computer. Pain scores, nausea scores and blood loss were similar in both groups, but patients receiving ibuprofen demanded significantly less morphine in the 24 h after surgery.

In addition to the control of symptoms associated with arthritis, non-steroidal anti-inflammatory drugs (NSAID) can be administered to relieve acute pain (Kantor, 1982). Although effective in the management of mild to moderate pain (Miller, 1981), there are conflicting reports as to the ability of NSAIDs to control postoperative pain. For example, several studies suggest that analgesia provided by an injectable preparation of acetyl salicylate is similar to that provided by parenteral morphine (Kweekel-De Vries et al., 1974; Cashman et al., 1985; Jones et al., 1985). Other investigators, however, were unable to demonstrate similar results (McAteer and Dundee, 1981).

Ibuprofen has been used in the treatment of postoperative pain and is as effective as, or superior to, aspirin, codeine, acetaminophen and codeine, or propoxyphene in this context (Miller, 1981; Dionne et al., 1983; Slavic-Svircev et al., 1984). In the earliest (although uncontrolled) study of the effects of ibuprofen on surgical wounds, decreases in both pain and inflammation were found (Choo and Lee, 1973). We are unaware of any previous double-blind studies using the regular administration of this agent to provide analgesia after abdominal gynaecological surgery.

PATIENTS AND METHODS

A double-blind, parallel-group, multiple dose study was approved by the Hospital Ethical Committee. Written informed consent was obtained from 71 patients scheduled to undergo lower abdominal gynaecological surgery. Patients with a history of peptic ulceration or gastrointestinal bleeding, asthma, or severe cardiac or respiratory disease were excluded.

Patients were randomly allocated to receive suppositories containing ibuprofen 500 mg ($n = 29$) or placebo ($n = 31$). The suppositories were administered, initially, 60–90 min before surgery, and then every 8 h for 24 h. All patients received an enema on the day before surgery and particular care was taken to ensure that each suppository was correctly inserted and not extruded.

The same anaesthetic technique and surgical incision (Pfannenstiel) were used in all patients. Premedication was with temazepam 30 mg administered at the same time as the first suppository. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and patients then received morphine 0.2 mg kg^{-1} i.v. Tracheal intubation was facilitated with a non-depolarizing myoneural blocking drug and the lungs were ventilated artificially with 33% oxygen in nitrous oxide and 0.5–1% halothane or 1–1.5% enflurane.

At the end of surgery, atropine 1.2 mg was

H. OWEN*, M.B., CH.B., F.F.A.R.C.S. (University Department of Anaesthesia); R. J. GLAVIN, M.B., CH.B., F.F.A.R.C.S. (Division of Anaesthesia); Royal Infirmary, Glasgow. N. A. SHAW, The Boots Co. PLC, Nottingham.

*Present address, for correspondence: Department of Anaesthesia, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia.

administered and residual neuromuscular blockade antagonized with neostigmine 2.5 mg. Following extubation of the trachea, patients were attached to an On-Demand Analgesic Computer (ODAC, Janssen Scientific Instruments, Beerse, Belgium) programmed to deliver 1-mg increments of morphine in 5% dextrose 5 ml i.v. The lockout interval was 2 min, giving a maximum permitted hourly dose of 30 mg, but the ODAC was set to warn attending staff when morphine 12 mg had been demanded in 1 h. Analgesia was self-administered for 24 h and the number of demands satisfied every hour was recorded. All patients were nursed on one ward where the staff are skilled in managing and monitoring patients receiving pain relief by patient-controlled analgesia (PCA).

Measurements of pain on a nine-point descriptive rating scale (described in figure 1) and nausea on a four-point scale (described in figure 3) were made by patients 6 and 24 h after surgery. Prochlorperazine 12.5 mg was administered to patients who vomited. Blood loss during surgery was measured by swab weighing. An attempt to assess the effect of ibuprofen therapy on haemostasis was made by measuring the area of bruising around the wound 3 days after surgery. Eleven patients did not complete the study, two because of a malfunction of the ODAC, five because of failure to administer a suppository at the correct time, three because surgery or anaesthesia was not standardized and one because of excessive histamine release caused by injection of morphine.

Statistical analysis

Demographic data were compared using an unpaired Student's *t* test. Differences in pain, nausea, administration of anti-emetic and morphine consumption were analysed with the Wilcoxon/Mann–Whitney test, and a Chi-squared test with Yates' correction was used to compare the incidence of vomiting in the two groups. A *P* value of less than 0.05 was accepted as being statistically significant.

RESULTS

Both groups were well matched for age, weight, height and operation (tables I and II). Patients became rapidly adept at managing their own pain relief and few patients experienced more than moderate pain (fig. 1). While the pain scores in the two groups were very similar, mean morphine consumption was different throughout the 24 h (fig. 2): patients receiving ibuprofen self-administered significantly less morphine in the postoperative period. Mean cumulative morphine consumption for patients receiving ibuprofen was 39.1 mg (SD 17.1 mg, range 9–128 mg); for the others 48.2 mg (SD 25.1 mg, range 13–129 mg).

TABLE I. *Demographic data. Mean ± SD and range*

	Ibuprofen	Placebo
n	29	31
Age (yr)	40.25±8.0	42.7±11.0
Weight (kg)	67.0±13.5	64.8±13.1
Height (cm)	161.7±6.5	160.8±8.0

TABLE II. *Number of patients undergoing surgery*

Type of surgery	Ibuprofen	Placebo
Hysterectomy	22	25
Ovarian cystectomy	3	3
Other surgery through Pfannenstiel incision	4	3

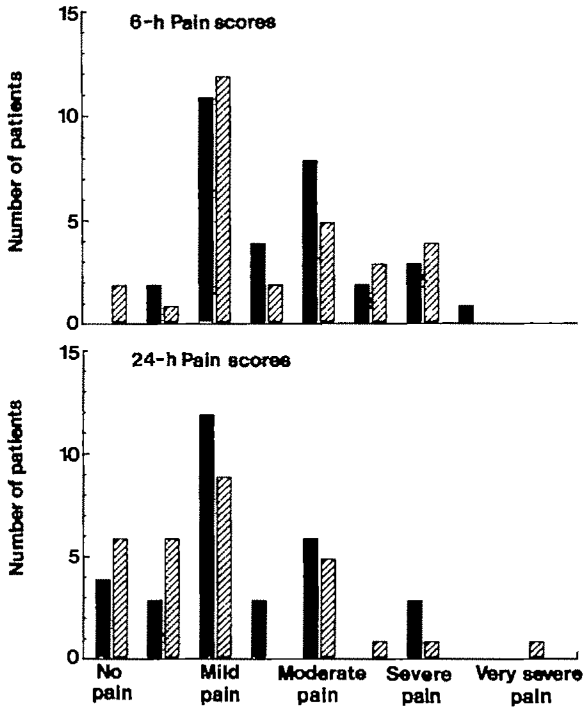

FIG. 1. Comparison of postoperative pain scores on an ordered categories scale. There are five described categories of pain and four unlabelled interval categories. Black columns = placebo; cross-hatched columns = ibuprofen.

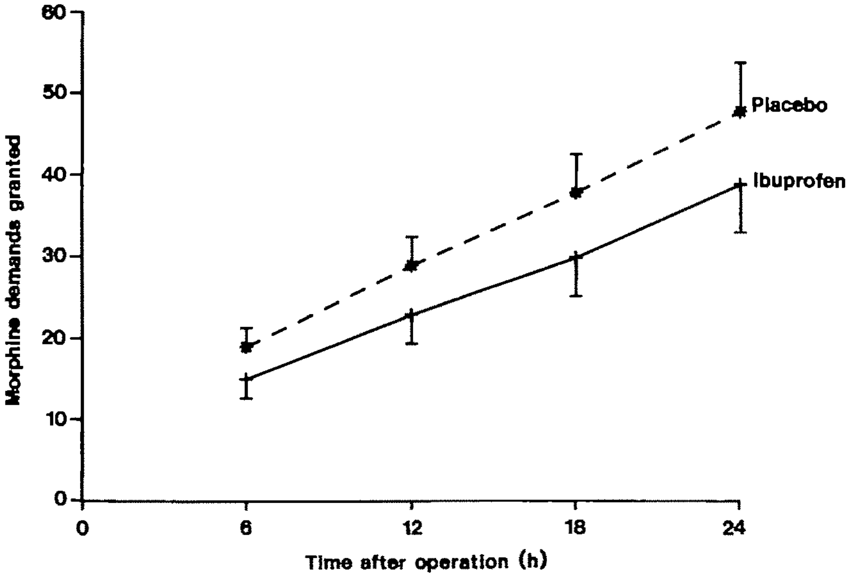

Fig. 2. Cumulative postoperative morphine consumption (mean ± SEM). The difference is significant ($P < 0.05$).

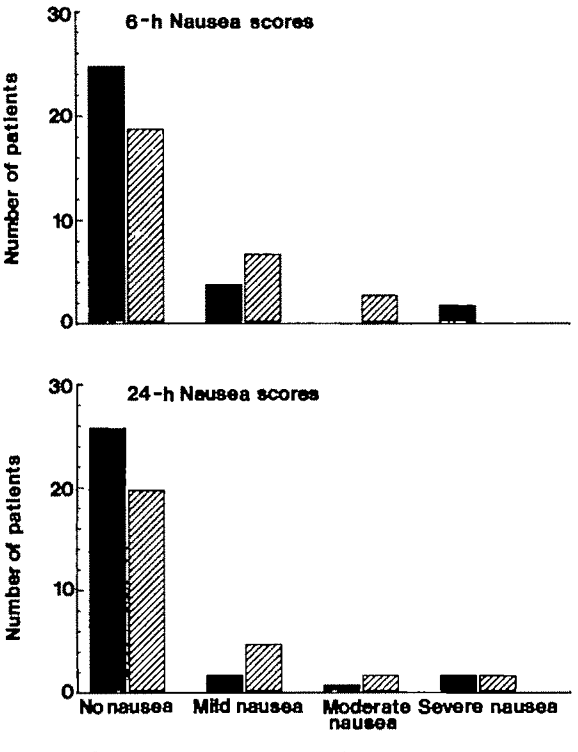

Fig. 3. Comparison of postoperative nausea scores on a four-point ordered categories scale. Black columns = placebo; cross-hatched columns = ibuprofen.

The incidence of nausea was low in both groups (fig. 3) although 79% of patients receiving ibuprofen and 58% receiving placebo vomited. This difference did not quite achieve statistical significance. There was no difference in the amount of anti-emetic administered to the two groups.

Intraoperative blood loss and the area of postoperative wound bruising were similar in both groups.

DISCUSSION

Patient-controlled analgesia is an effective method of relieving postoperative pain (Graves et al., 1983; Rosen, 1984). PCA is an "active" system (Welchew, 1983) and many patients will still experience some pain. If "passive" background analgesia is also provided, then any reduction in active PCA demands will be a measure of the efficacy of the background analgesic. We have found that the regular administration of ibuprofen reduced the demand for morphine from an ODAC by 20%. A similar method for measuring analgesic potency of an NSAID has been reported previously (Jones et al., 1985) but, in contrast to these workers, we have used a short lockout interval and have not limited morphine consumption beyond the physical constraints of the lockout interval, that is a maximum dose of 30 mg h^{-1}, and we have not, therefore, relied on nursing staff to give discretionary i.m. injections of analgesic.

Ibuprofen was administered rectally because a parenteral formulation is not yet available and oral therapy was thought to be inappropriate in the perioperative period. The suppository formulation of ibuprofen used is widely available in Europe and, in common with other propionic acid derivatives, it is absorbed efficiently, although more slowly than by the oral route (de Boer et al., 1982; Boots Co. PLC, 1985). Therapy was initiated before operation because previous work suggested a slow onset time of analgesia from ibuprofen of around 3 h (Slavic-Svircev et al., 1984) and the preoperative administration of ibuprofen has been shown to suppress postoperative dental pain (Dionne et al., 1983). The reduction in morphine requirement in patients receiving ibuprofen was present throughout the 24 h after surgery, suggesting that the subsequent regular therapy provided a stable level of background analgesia.

In most studies on analgesics, pain scores are used to differentiate the potency of the agent under scrutiny. Apart from difficulty in the analysis of different pain scores and different drug doses, the ethics of subjecting one group of patients to more pain than another is questionable. Using PCA, all patients can titrate themselves to a "low-pain" endpoint, and only the different analgesic requirements of the groups need be considered further. PCA was originally developed to provide an objective measurement of pain (Sechzer, 1968); however, there is a large inter-individual variation in morphine consumption and conclusions cannot be drawn from measurements from small samples.

Mean pain scores were low in both groups, but a few patients in each group appeared to limit their morphine intake because of the nausea or vomiting associated with demanded doses. There was, however, no correlation between pain and nausea scores in either group. An ordered categories scale was used to avoid the difficulties reported when using a visual linear analogue to measure pain after surgery (Grossi, Borghi and Montanari, 1985). Both groups received a similar amount of anti-emetic but, despite administering less morphine, the incidence of vomiting was not reduced in the group receiving ibuprofen. If oral therapy had been used, the high incidence of vomiting might have reduced the amount of drug absorbed.

Control of cancer pain by oral narcotic therapy can be significantly improved without an increase in adverse effects by concurrent administration of ibuprofen (Ferrer-Brechner and Ganz, 1984; Weingart, Sorkness and Earhart, 1985). In this study there was a reduction in opioid requirement by patients receiving ibuprofen to achieve pain scores similar to those in the placebo group. If ibuprofen is administered in combination with traditional and ineffective (Leading Article, 1978) pulsed opioid therapy after surgery, it may improve the overall relief of pain. Balanced anaesthesia is an integral part of clinical practice and there may also be a place for balanced analgesia after surgery.

In common with other NSAID, ibuprofen has side effects from its inhibition of prostaglandin synthesis (Miller, 1981). We have paid particular attention to any effect that may inhibit blood coagulation, but in the dose used ibuprofen affected neither intraoperative blood loss nor postoperative haemostasis — as measured by area of wound bruising — adversely.

In conclusion, the regular perioperative administration of ibuprofen significantly reduced postoperative opioid requirements. There were no adverse effects apparent with this therapy.

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CRICOID PRESSURE WITH OR WITHOUT THE "CRICOID YOKE"

E. G. LAWES

SUMMARY

The performance of cricoid pressure was studied in three groups of medical personnel likely to be involved in its application using the cricoid yoke and a test rig. The instrument enabled individuals who had no previous experience in the application of cricoid pressure to achieve results as good as those obtained by experienced anaesthetic staff. Furthermore, the instrument improved the consistency of the applied force in all groups, particularly if cricoid pressure was required for sustained periods of 30 s or more.

The application of cricoid pressure (Sellick, 1961) would appear to be, at best, a haphazard manoeuvre even when applied by trained individuals (Howells et al., 1983). An instrument has been described that enabled experienced assistants to provide consistent and reproducible cricoid pressure during the rapid sequence induction of anaesthesia, and was evaluated in patients presenting for elective Caesarean section (Lawes et al., 1986).

The present study was undertaken to determine whether untrained staff with no previous experience could, by using this instrument, provide as safe and adequate cricoid pressure as the best efforts of trained staff. The results of attempts made freehand, and those obtained whilst using the yoke on a test rig were compared with similar best efforts of two groups of trained anaesthetists and their assistants.

MATERIALS AND METHODS

Participants ($n = 81$) were allocated to one of three groups. The first group (trained A) consisted of consultant anaesthetic staff and anaesthetic senior registrars. The second group (trained B) consisted of anaesthetists in training, anaesthetic and intensive care nurses, and operating department assistants who provided cricoid pressure regularly. The final group (novice) consisted of theatre, intensive care and accident room nursing and ambulance personnel who had never, or only rarely, assisted at intubation. This group represented those individuals with very little or no previous experience in the application of cricoid pressure, but who may be called upon in an emergency to assist with patients who are at risk of inhaling stomach contents.

The first two groups were asked to apply cricoid pressure "freehand' to a Royal Free intubating model as if they were performing the manoeuvre during a rapid sequence induction. They were asked to sustain the applied force until instructions were given to release cricoid pressure. An interval of 30–45 s was allowed to elapse to account for the period of tracheal intubation before instructions to release were given.

Subjects in the third (novice) group, having been instructed in the location of the cricoid cartilage and the purpose of the manoeuvre, were asked to apply cricoid pressure in the same manner. The basic instruction given to these individuals was to apply a backwards force at the site of the cricoid cartilage using two fingers and the thumb. They were asked to apply as much force as they felt would be required to produce tolerable pain if the same force was applied to the bridge of the nose, and were told to maintain this pressure until instructed to release it. All groups were asked to perform the freehand manoeuvre three times.

All subjects were then instructed how to apply cricoid pressure correctly using the cricoid "yoke". With the instrument placed over the region of the cricoid cartilage, both thumbs were

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E. G. Lawes, M.B.B.S., F.F.A.R.C.S., Sir Humphry Davy Department of Anaesthetics, Bristol Royal Infirmary, Bristol BS2 8HW.

placed over the tips of the wings, and backwards and slightly outwards pressure applied until the light and buzzer were activated. This position was maintained throughout the "intubation" interval until instructions to release were given. The subjects were told to ensure that they exerted no flexing motion on the instrument as this could produce a premature activation of the signals. Three attempts were made to obtain adequate cricoid pressure using the yoke.

In order to measure the force applied by the subjects in their performance of cricoid pressure, a Royal Free Hospital intubation model was mounted on a spring weighing scale. Before the investigation began, the scales were calibrated to read up to 5.5 kg at 100-g intervals, with an accuracy of ±100 g. The cricoid yoke was calibrated to ensure that, once the optimum force of 44 Newtons had been achieved (equivalent to 4.5 kg), the user was informed by means of both a light and a buzzer. The force required to activate these signals was adjustable by means of a screw gauge that altered the position of the contacts (fig. 1).

The mean, maximum/minimum and standard deviation of the applied forces obtained from the attempts made "freehand" and with the yoke, were calculated for each of the three groups. Student's *t* test was used to determine if statistically significant differences were demonstrable.

RESULTS

Eleven consultants and senior registrars were classified as having completed their training for the purposes of this investigation (trained A). Thirty-five subjects each, fell under the classification of "trained B" or "novice".

The measured values produced by the "freehand" application of cricoid pressure and using the yoke are shown in table I and figure 1. There was no statistically significant difference between the cricoid pressure applied freehand and that applied using the yoke in trained group A, nor was there any difference between the trained group A and the newly taught novice group when applying freehand pressure. However, there was a significant difference between the novice group applying freehand pressure and the pressures achieved when they used the yoke ($P < 0.01$). This difference can be accounted for by the frequency with which inadequate pressure was generated during the freehand application of force, a feature not evident when cricoid pressure was applied using the yoke.

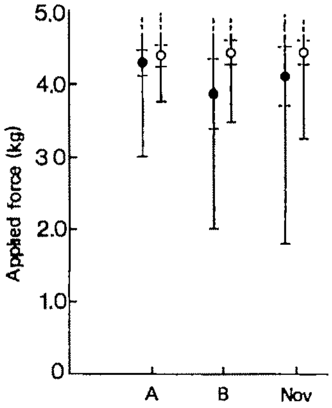

FIG. 1. Results achieved on the test rig (● = freehand; ○ = cricoid yoke). A = trained group A; B = trained group B; Nov = novice. The mean, standard deviation and range of the results are included for each group. The applied force is represented by the weight measured on the weighing scale. (To convert from kg to Newtons multiply by 9.81.)

The forces applied freehand by the trained group B were significantly different when compared with the forces achieved by trained group A ($P < 0.001$). The differences between the freehand and yoke pressures in trained group B were also significant ($P < 0.001$). Significant differences were also evident between the freehand performances of the trained group B and the recently taught novice group ($P < 0.02$).

Comparison of the novice group applying cricoid pressure with the aid of the yoke against the freehand performance of the trained group B demonstrated significant differences ($P < 0.001$).

Cricoid pressure as measured on the test rig was applied equally well by all groups when using the yoke; no significant differences could be detected between any of the groups.

TABLE I. *Force of cricoid pressure applied freehand or using the yoke. Values are mean ± SD (range)*

Group	Freehand (kg)	Yoke (kg)	*P*
Trained A	4.3±0.69 (3–≥5)	4.4±0.3 (3.75–≥5)	ns
Trained B	3.9±0.98 (2–≥5)	4.4±0.36 (3.5–≥5)	< 0.001
Novice	4.1±0.8 (1.8–≥5)	4.4±0.37 (3.2–≥5)	< 0.01

DISCUSSION

The efficacy of cricoid pressure has been demonstrated in children (Salem, Wong and Fizzotti, 1972) and adults (Fanning, 1970). Indeed Rosen (1981) has described it as the linch pin of the rapid sequence induction of anaesthesia. No significant adverse consequences have been reported as a result of its use (Sellick, 1982). Inhalation of gastric contents resulted in the deaths of 13 mothers in England and Wales, and of three in Scotland, over the period 1972–75. In five instances cricoid pressure was applied incorrectly and in seven it was not applied at all (Moir, 1980). Howells and co-authors (1983) demonstrated that, despite the pre-eminence of this manoeuvre in the rapid sequence induction, its application was, in general, performed badly. Wraight, Chamney and Howells (1983) were able to quantify the forces required such that adequate cricoid pressure would be applied to all but the most exceptional patients presenting for emergency surgery.

A measuring device such as the yoke used in this study enabled the novice to provide cricoid pressure which was not significantly different from that obtained by senior anaesthetic staff. The ability to sustain adequate cricoid pressure for prolonged periods was facilitated by the instrument in all groups tested.

The yoke was calibrated to signal when a force of 4.5 kg had been applied to the area of cricoid cartilage. This is approximately 44 Newtons, and was the force Wraight, Chamney and Howells (1983) determined would be sufficient to protect the majority of patients. Their is no absolute value to the force required for the correct application of cricoid pressure and this value represents the optimum force in the view of those authors. It would be reasonable to a expect a range of forces that would occlude the oesophagus effectively in the event of failure of the lower oesophageal sphincter.

The measurement of the forces used for the freehand application of cricoid pressure revealed a steady decline in the applied force when the manoeuvre was sustained for more than 30 s. An initially satisfactory freehand application near to or at the optimum value deteriorated usually to an inadequate value towards the end of the intubation interval. This observation was made in all groups, although it was least apparent in the trained group A. This phenomenon is probably the explanation for the significant difference between the freehand and yoke pressures generated by the novice group.

There would appear to be no need for trained group A, as a whole, to use this or any similar device in order to apply proper cricoid pressure, although some evidence of inability to sustain cricoid pressure was obtained even in this group.

Trained group B demonstrated a significant failure rate in achieving adequate freehand cricoid pressure. Although the mean pressure obtained was satisfactory, the range of applied force was large, a result similar to that noted by Howells and colleagues (1983).

The novice group achieved an adequate "freehand" cricoid pressure initially. However, improvement could be demonstrated in sustaining the correct force when the yoke was used.

The instruction to apply as much force as would be required to produce just tolerable pain if the same force was applied to the bridge of the nose, would appear to be a good guide to the force required to achieve adequate cricoid pressure (Mehrotra and Paust, 1979).

The instrument was calibrated to signal when a force equivalent to weight of 4.5 kg was achieved. The applied force at which the signals could be activated was reduced by applying a flexing or folding moment to the wings. Evidence of this flexing motion is represented by the minimum force detected during the application of the yoke—3.2 kg. The slight lateral displacement of the wings detailed in the operating instructions (in addition to the backwards force) was to circumvent this problem.

In conclusion, the use of the cricoid yoke to measure forces applied during the application of cricoid pressure was beneficial. It ensured an adequate initial force and the consistency of the force applied over intervals of 30 s or more was improved. Any tendency to relax the applied force was evident immediately. The instrument enabled individuals with no previous experience in the application of cricoid pressure to achieve as good results as properly applied freehand efforts obtained by experienced anaesthetic staff.

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INTERACTION BETWEEN THIOPENTONE AND SODIUM VALPROATE

An In Vitro *and* In Vivo *Study*

L. AGUILERA, R. CALVO AND R. C. GARCIA

SUMMARY

The effect of sodium valproate on the binding of thiopentone to serum protein was studied in vitro. *In the absence of valproate the unbound fraction of thiopentone was 15.2±0.64%, but with concentrations of valproic acid in excess of the therapeutic range, it increased to 22.42±1.65%. Scatchard plots for thiopentone in the absence and presence of valproate were investigated also. The barbiturate was bound by one group of binding sites with the association constant,* $K_a = 2.81 \times 10^3$ *litre* mol^{-1} *and the number of binding sites* (n) = *2.3. There was a marked decrease in this association constant in the presence of valproic acid* ($K_a = 1.82 \times 10^3$ *litre* mol^{-1})*, but without significant change in the number of binding sites* (n = *2.13*)*. Additionally, the effect of administration of sodium valproate i.v. on thiopentone anaesthesia was examined in rabbits. The recovery time from thiopentone was markedly longer in the presence of the anticonvulsant drug* (*17.0 min* v. *37.1 min*).

The binding of drugs to plasma proteins is a complex, dynamic process subject to numerous influences. Plasma albumin is the primary determinant of the binding of acidic drugs, but other substances in plasma, particularly highly bound drugs, may compete for binding sites, leading to the dissociation of the protein–drug complex and to an increase in the concentration of free drug. The consequences of such displacement are variable as, in most cases, the kinetic changes are transient and a new equilibrium with restored concentrations of free drug in plasma is achieved readily (Sellers, 1979). However, even the temporary increase in the concentration of free drug in plasma may result in an increase in pharmacological effect which may be of clinical significance (McElnay and D'Arcy, 1983). Changes in the plasma protein binding of anaesthetic agents may influence markedly their disposition, elimination and, therefore, their main pharmacological effect (Brodie, Kurz and Schanker, 1960). Alterations in the pharmacokinetics of thiopentone have been described in rats pretreated with sulphadimethoxine (Ghoneim et al., 1976), and a decrease in anaesthetic dose of thiopentone as well as an increase in the rapidity of induction of anaesthesia with midazolam have been reported in patients treated with displacing agents (Csögör and Kerez, 1970; Dundee, Halliday and Loughran, 1984).

The anticonvulsant drug valproic acid is extensively bound to plasma proteins (Gugler and Mueller, 1978; Cramer and Mattson, 1979) and has been implicated in several drug interactions (Fleitman et al., 1980). However, interaction between valproic acid and i.v. anaesthetic agents has not been described. The purpose of our study was to evaluate the effect of sodium valproate on the plasma protein binding of thiopentone *in vitro* and to assess the influence of pretreatment with this antiepileptic agent on the hypnotic and anaesthetic effects of thiopentone in the rabbit.

MATERIALS AND METHODS

Animals

New Zealand White rabbits weighing 3–4 kg were used: they were kept in individual, well-

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L. AGUILERA, M.D., Servicio de Anestesia y Reanimación, Hospital de Galdakao, Vizcaya, Spain. R. CALVO, PH.D., Departamento de Farmacologia, Facultad de Medicina, Universidad del País Vasco, Leioa, Spain. R. CARLOS GARCIA, M.D., Departamento de Anestesiologia y Reanimacion, Hospital clínico de San Cecilio, Falcultad de Medicina, 18012 Granada, Spain.

Correspondence to R.C.G.

ventilated cages for at least 10 days before the study.

Plasma protein binding of thiopentone

Plasma protein binding of thiopentone was measured in blood samples from eight rabbits. In each, blood was drawn by ear artery puncture and three 2-ml aliquots were used. Sodium valproate was added to two of the aliquots (final concentrations 100 and 500 µg ml^{-1}) and 15 min thereafter thiopentone was added to all three to yield a concentration of 25 µg ml^{-1}. Ultrafiltrates of plasma were obtained using a U-shaped cellophane tube and a centrifugal force of 600 *g* for 45 min. Thiopentone concentration in the ultrafiltrate was measured by the method of Brodie, Mark and Papper (1950).

The interaction of thiopentone with plasma proteins was measured using Scatchard plots (Scatchard, 1949). The equation $r/D = n.K_a - r.K_a$ was used; r is the number of moles of bound drug per mole of albumin, n is the number of binding sites, K_a is the association constant for the drug–protein complex, and D is the molar concentration of free drug.

Effects of thiopentone

Two groups of five rabbits were used. In one group, the animals received a dose of valproate 50 mg kg^{-1} i.v. 1 min before the administration of the thiopentone. In the other (control) group, rabbits received a corresponding volume of physiological saline 1 min before the injection of the thiopentone. In all rabbits, thiopentone was injected using the same vein as that for the pretreatment, at a dose of 30 mg kg^{-1}, with an injection time of 30 s. The duration of anaesthesia was evaluated as the interval between the time of the thiopentone administration and the recovery of the righting reflex. This was assessed by placing the rabbit on its back and the end point was recorded when the animal regained a position with its feet on the ground. Loss of the corneal reflex was established by means of light stimulation with a cotton swab repeated every 5 s during the injection of the thiopentone. Reactions to painful stimuli were assessed twice at 30-s intervals, upon completion of the injection of the thiopentone. Complete sensory blockade was considered present if the animal did not attempt to withdraw the hind-legs in response to pinching of the food-pads with pincers.

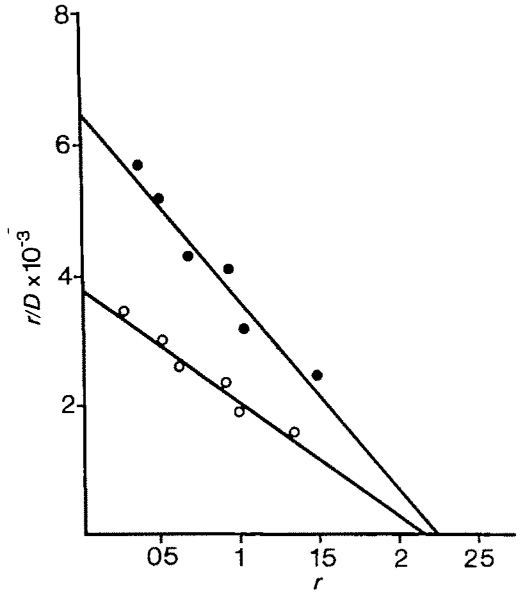

FIG. 1. Scatchard plot for the binding of thiopentone in plasma in the absence (●) and presence (○) of sodium valproate. r = Number of moles of bound drug per mole of albumin; D = molar concentration of free drug. Thiopentone only: $K_a = 2.81 \times 10^3$ litre mol^{-1}, $n = 2.3$; thiopentone plus valproate: $K_a = 1.82 \times 10^3$ litre mol^{-1}, $n = 2.13$.

TABLE I. *Effect of sodium valproate on plasma free fraction of thiopentone* in vitro (*mean* ± *SEM*)

		Concentration of added valproate	
	Control ($n = 8$)	100 µg ml^{-1} ($n = 8$)	500 µg ml^{-1} ($n = 8$)
Free fraction of thiopentone (%)	15.12 ± 0.64	22.42 ± 1.65	45.42 ± 2.27

RESULTS

In vitro studies

The addition of sodium valproate to rabbit plasma *in vitro*, decreased the binding of thiopentone, also added *in vitro*. The free fraction of thiopentone in control samples was 15.1 % and the percentages increased to 22.4 and 45.6 % in samples containing valproate 100 and 500 µg ml^{-1}, respectively (table I). Scatchard plots for thiopentone binding showed a decrease in the association constant (from 2.81×10^3 to 1.82×10^3 litre mol^{-1}) without any change in the number of binding sites, in the samples containing sodium valproate (fig. 1).

TABLE II. *Effects of sodium valproate 50 mg kg^{-1} i.v. on recovery time, dose inducing loss of corneal reflex, and reaction to stimuli after thiopentone 30 mg kg^{-1} i.v. (mean + SEM).* *P < 0.001

	Recovery time (min)	Corneal reflex loss (mg kg^{-1})	Painful reaction
Control rabbits ($n = 10$)	17.0±0.51	20.1±1.1	All
Valproate-pretreated rabbits ($n = 10$)	37.1±3.4*	16.3±1.6	None

In vivo studies

Pretreatment of rabbits with sodium valproate resulted in a marked increase in the duration of thiopentone anaesthesia (table II). Mean time to recovery (±SEM) was 17±0.5 min in the control group and 37±3.4 min in the valproate group ($P < 0.001$). On the other hand, there were no clear differences in the dose of thiopentone needed to induce the loss of the corneal reflex (20.1±1.1 mg kg^{-1} (control) *v.* 16.3±1.6 mg kg^{-1} (valproate)), but all the valproate-pretreated animals showed no reaction to painful stimuli, whereas all control rabbits responded.

DISCUSSION

The importance of binding to plasma proteins in the pharmacokinetics and pharmacodynamics of i.v. anaesthetic agents has been known for many years. Pagnini and co-workers (1971) reported that prior administration of sulphonamides, salicylic acid, doxycycline and p-aminosalicylic acid increased significantly pentobarbitone sleeping time in mice. Chaplin, Roszkowski and Richards (1973) found that high doses of aspirin, phenylbutazone or naproxen given to rats that had just regained the righting reflex after an anaesthetic dose of thiopentone caused the animals to fall asleep again. The reappearance of sleep correlated with a marked increase in the concentration of unbound thiopentone in plasma, suggesting a displacement of the barbiturate from its binding sites on plasma proteins by the anti-inflammatory agents. Furthermore, Ghoneim and coworkers (1976) found that when ^{14}C-thiopentone was injected i.v. to rats 1 min after pretreatment with sulphadimethoxine 30 mg kg^{-1} i.v., free thiopentone in plasma and thiopentone concentration in the brain were increased. More recently, a relationship between serum albumin concentrations and induction time after midazolam has been reported (Reves, Newfield and Smith, 1981), and the role of plasma protein binding in the response to this benzodiazepine has been stressed further by the finding that pretreatment with highly bound drugs, such as aspirin or probenecid, greatly reduces onset time in man (Dundee, Halliday and Loughran, 1984; Halliday et al., 1984).

Sodium valproate is bound strongly to plasma albumin and the displacement of other highly bound drugs has been described *in vitro* as well as *in vivo* (Dhillon and Richens, 1981, 1982). The results of our study show that valproate can displace thiopentone from its binding sites on albumin and influence its pharmacological effects. A decrease in the plasma protein binding of thiopentone could result in greater accessibility to the central nervous system and some decrease in the rate of distribution owing to reduced affinity. In our study, the dose of thiopentone needed to achieve the loss of the corneal reflex tended to be lower in pretreated rabbits, although the difference between the groups did not achieve significance. On the other hand, reactivity to painful stimuli was definitely less in the animals receiving valproate and, in addition, there was a marked increase in recovery time. This could hardly be the result of the inhibition of thiopentone metabolism by valproate as, at this time, metabolic loss is minimal (Burch and Stanski, 1981). Therefore, it seems likely that the *in vitro* displacement of thiopentone by valproate does occur *in vivo*, leading to the observed increase of anaesthetic effect. Even if the doses and concentrations of sodium valproate used in this study were higher than those that apply in man, they were within the anticonvulsant range in the species studied (Pei et al., 1983).

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COMPARISON BETWEEN PRESSURES MEASURED FROM THE PROXIMAL EXTERNAL JUGULAR VEIN AND A CENTRAL VEIN

MAHESH V. SHAH, E. A. SWAI AND I. P. LATTO

When central venous catheters are inserted through superficial arm or external jugular veins, trauma is minimized at the time of insertion. These routes are particularly appropriate for the clinician who wishes to avoid the potential complications of the internal jugular or the subclavian routes. Veins in the arm are commonly used in anaesthetic practice, although it appears that the external jugular route is becoming more popular. In about 30% of patients, however, the catheter fails to advance from the external jugular vein into the superior vena cava (Deitel and McIntyre, 1971; Malatinsky et al., 1976; Riddell, Latto and Ng, 1982). Possible causes for the failure are: a small venous plexus present at the level of the clavicle (Blitt et al., 1974); the acute angle of entry of the external jugular vein to the subclavian vein; or the tip of the catheter becoming lodged in the ostium of a small tributary. If the catheter fails to advance, the question arises: is it necessary to seek central placement by another route or is the pressure indicated via the "stalled" catheter a good enough approximation of central venous pressure?

This study was designed to compare the external jugular venous pressure, measured from the point at which the catheter failed to advance, with true central venous pressure. The influence of the position of the head on external jugular pressure was investigated also.

PATIENTS AND METHODS

Twenty patients were studied before elective cardiac surgery. Anaesthesia was induced and mechanical ventilation of the lungs commenced. The investigation was performed while the patients were stable with respect to the cardiovascular system. The external jugular vein was cannulated percutaneously (Piggy Back catheter No. 3316, Wallace, Colchester, Essex) with the patient tilted in a 20° head-down position. The left or right external jugular veins were used in alternate patients. A catheter was threaded through the cannula. The catheter had a round occluded tip and two side holes (Farman, 1976). If the catheter advanced centrally the patients were excluded from the study. In patients in whom resistance was encountered, the catheter was withdrawn approximately 0.5 cm and free flow of blood confirmed. The cannula was then removed from the vein and the patient was returned to the horizontal position. No force was used to advance the catheter as this can result in kinking and difficulty in removal (McKenzie and Latto, 1981). The position of the catheter tip was confirmed by x-ray after surgery.

SUMMARY

Mean venous pressures were measured in 20 patients in whom a catheter, inserted via the external jugular vein, failed to pass centrally. The catheter used had a rounded end and two side holes. Pressures were measured with the patient's head in three different positions. The pressures were compared with the central venous pressures measured from a catheter inserted through an antecubital vein (and confirmed to be placed centrally). In all patients the differences between the mean pressures from the two sites were all within 3 mm Hg and were not influenced by alteration in head position or the side of jugular catheterization.

MAHESH V. SHAH, M.B., B.S., L.R.C.P., M.R.C.S., F.F.A.R.C.S.; E. A. SWAI, F.F.A.R.C.S.; I. P. LATTO, M.B., B.S., F.F.A.R.C.S.; Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

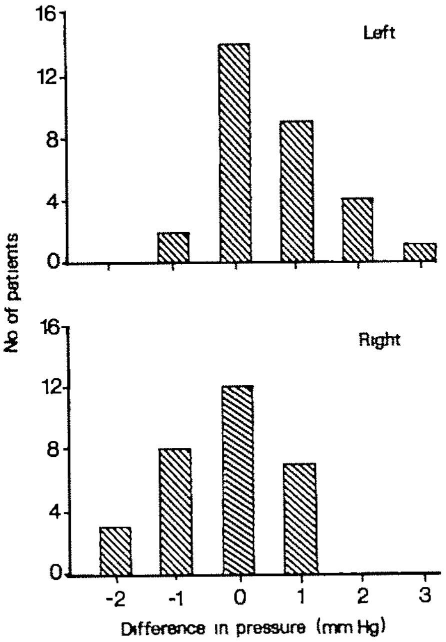

FIG. 1. Individual differences between the mean external jugular venous pressures (left and right) and the corresponding mean central venous pressures (EJVP – CVP) (mm Hg) (all head positions).

A Drum Cartridge catheter (Abbott Venisystems No. 4719) was then passed into the superior vena cava via a vein in the antecubital fossa. Its position was assessed by x-ray and the catheter adjusted so that the tip was approximately 2 cm below the lower border of the clavicle (Greenall, Blewitt and McMahon, 1975).

The catheter in the external jugular vein was connected to a previously calibrated pressure transducer (Hewlett–Packard 1280C) and the mean pressure measured with the head turned to the right, to the left and while positioned in the mid-line. Mean central venous pressures were also recorded after each of these readings by connecting the Drum Cartridge catheter to the same pressure transducer.

The mean external jugular venous pressures of each patient were compared with the corresponding mean central venous pressures using the Student's t test for paired data.

RESULTS

X-rays showed that the tip of the "stalled" catheter in the external jugular vein lay roughly at the level of the clavicle in all patients.

The range of mean venous pressures encountered was from −2 to +9 mm Hg (+14 mm Hg in one patient).

The mean left external jugular venous pressures (EJVP) tended to be slightly greater than the mean central venous pressures (CVP) (fig. 1). The mean of the differences between the left EJVP and the CVP in individual patients was statistically significant with the head in the central position ($P < 0.05$) (table I). There were similar findings with the head turned to the right ($P < 0.02$). However, the differences in mean pressures in individual patients were small (fig. 1). At most, the mean left EJVP was greater than the mean CVP by 3 mm Hg in one instance and was less than the mean CVP by 1 mm Hg in two instances (fig. 1).

The mean right EJVP values tended to be slightly less than mean CVP values (fig. 1). Differences were not statistically significant with any head position (table I) and the individual differences were small. At most, the mean right EJVP was greater than the mean CVP by 1 mm Hg in seven instances and was less than the mean CVP by 2 mm Hg in three instances (fig. 1).

DISCUSSION

Although some of the differences between the mean EJVP and the mean CVP values were statistically significant, none was of clinical signi-

TABLE I. *Differences between the external jugular venous pressures (left and right) and the corresponding central venous pressures: (EJVP-CVP) (mm Hg), related to head position (to left, central, or to right)*

	Left			Right		
	To left	Central	To right	To left	Central	To right
n	10	10	10	10	10	10
Mean of individual differences	0.60	0.40	0.80	−0.05	−0.25	−0.40
SE of mean difference	0.43	0.16	0.25	0.32	0.31	0.27
t	1.41	2.45	3.21	0.16	0.81	1.50
P	> 0.1	< 0.05	< 0.02	> 0.4	> 0.4	> 0.1

ficance. Perhaps the statistically significant differences were attributable to a difference in the height of the vessels above the table, or to differences in resistance between the two external jugular veins and the superior vena cava.

Previous workers (Briscoe, 1973; Stoelting, 1973) have shown that a short (5-cm) cannula placed in the external jugular vein could not be relied upon to provide accurate measurements of central venous pressure. This study demonstrates that, if a catheter with an occluded end and two side holes is inserted to the external jugular vein and fails to advance beyond the clavicle, a clinically reliable measurement of mean central venous pressure can be obtained.

The clinical significance of the present findings is that, in the 30% of patients in whom a catheter fails to advance into the superior vena cava, reliable recordings of mean central venous pressure can be obtained. It is common practice to remove external jugular catheters which fail to pass centrally. Alternatively, the catheter can be removed and a J-wire (Blitt et al., 1974) can be passed through the cannula and an attempt made to pass the wire centrally. Data are available on the success rate for central placement with such wires in adults (Blitt et al., 1974; Schwartz et al., 1981) and children (Humphrey and Blitt, 1982). However, there are no data regarding successful central placement rates with J-wires in patients in whom conventionally introduced catheters fail to pass centrally. This aspect is currently under investigation.

A previous study using the same catheters (Wallace Piggy Back) inserted for a short distance to the internal jugular vein demonstrated that accurate pressure measurements can be obtained (Reynolds, Cross and Latto, 1984). However, these peripheral internal jugular pressures were, on occasions, greater than central venous pressures when using a cannula if the patient's head was turned towards the side of cannulation. The position of the patient's head did not have a clinically significant influence on the pressure measurements in any patient in the present study.

However, there are situations in which catheters, stuck at the level of the clavicle, may not provide acceptable measurements of central venous pressure. In catheters with a single distal opening, occlusion may occur against the wall of the vein. The catheter might pass into a small tributary of the external jugular vein or, if excessive force is used, the catheter may become kinked. When infusing potent drugs it should be confirmed that the catheter is placed i.v. Particular care should be taken to ensure that such catheters are fixed securely.

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A SIMPLE ATRACURIUM INFUSION REGIMEN FOR INTRA-ABDOMINAL SURGERY

J. R. SNEYD

SUMMARY

Atracurium was used to provide relaxation for intra-abdominal surgery in 15 patients. The regimen comprised an initial bolus (0.4 mg kg^{-1}) followed by an infusion (0.3 mg kg^{-1} h^{-1}) from 10 min after induction until closure of the peritoneum. Average duration of infusion was 80 min (range 48–166 min). This regimen provided satisfactory relaxation in 13 patients; two patients required one additional bolus of atracurium. Fourteen patients showed a sustained tetanic response to 50-Hz stimulation at the end of surgery and in these neuromuscular blockade was not antagonized. One patient required antagonism following very rapid closure of the abdomen.

The pharmacokinetic and pharmacodynamic characteristics of atracurium make it an attractive agent for use as a continuous infusion. Non-enzymic degradation suggests that cumulation is unlikely, but this has yet to be confirmed. Since the elimination of atracurium is almost independent of hepatic and renal function (Neill, Chapple and Thompson, 1983), such a technique would be particularly applicable to sick and debilitated patients.

The objective of this study was to explore the feasibility of using a single dose regimen in conjunction with simple monitoring equipment.

PATIENTS AND METHODS

Fifteen consecutive patients scheduled for gynaecological or general surgical procedures (table I), were studied. Nine patients were ASA Class I, two were ASA Class II and four were ASA Class III. Three of the operations were emergency procedures.

All patients received premedication: those in ASA Classes I and II received papaveretum 10–15 mg and hyoscine 0.2–0.3 mg; those in ASA Class III were given pethidine 50–100 mg.

Anaesthesia was induced with thiopentone (mean 253 mg) followed, in all but one patient, by droperidol (mean 8.5 mg) and fentanyl (mean 267 µg). Patient No. 9 (table I) received alfentanil and no droperidol. Anaesthesia was maintained with 66 % nitrous oxide in oxygen. Tachycardia, hypertension or sweating were treated by the addition of 0.6 % enflurane (usually only for a few minutes).

Atracurium 0.4 mg kg^{-1} was given as a bolus immediately after the thiopentone and flushed in with isotonic saline. Intubation was performed at 2 min. Ten minutes after induction, an infusion of atracurium was commenced. Atracurium 50 mg was diluted to 50 ml with 0.9 % saline and infused at an hourly rate of 0.3 mg kg^{-1} using an electric syringe pump (Vickers) connected to a three-way tap in a peripheral i.v. infusion as close to the patient as possible. Infusion was discontinued on peritoneal closure.

Intubating conditions were assessed by the scale of Twohig, Ward and Corall (1983).

At 5-min intervals throughout the procedure the surgeon was asked to classify abdominal relaxation as satisfactory or unsatisfactory. A small bolus of atracurium was given if appropriate (table I).

Neuromuscular blockade was monitored intermittently using a hand-held peripheral nerve stimulator (Wakeling Instruments) with supramaximal "train-of-four" and tetanic stimuli applied over the facial nerve. No attempt was made to adjust the infusion to attain a specific degree of reduction in the train-of-four response.

J. ROBERT SNEYD, F.F.A.R.C.S., Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Present address: 44 Penwortham Road, London SW16 6RE.

TABLE I. *Patient details and drug doses. T = thiopentone; D = droperidol; F = fentanyl; E = enflurane; Inf = infusion time; Close = closure time*

Patient No.	Sex	Age (yr)	Weight (kg)	ASA Class	Procedure	T (mg)	D (mg)	F (mg)	Inf (min)	Close (min)	E?	Notes
1	F	77	51	III	Exploratory	250	5.0	0.25	63	20	Yes	
2	F	37	50	I	Tubal surgery	400	5.0	0.3	76	11	No	
3	M	55	65	I	Cholecystectomy	400	7.5	0.2	66	13	No	
4	F	59	70	I	Hysterectomy	250	10.0	0.35	48	11	Yes	
5	F	84	34	III	R. hemicolectomy	200	4.0	0.1	60	12	Yes	
6	F	47	73	I	Hysterectomy	200	7.5	0.2	66	13	No	
7	F	55	95	I	Cholecystectomy	250	10.0	0.5	166	31	Yes	Atracurium 10 mg for hiccup
8	F	53	69	I	Hysterectomy	250	7.5	0.25	52	13	No	
9	F	87	50	III	Rectopexy	150			93	12	No	Alfentanil 1 mg at induction
10	F	64	50	II	Ovarian cyst	250	5.0	0.2	70	12	No	
11	M	72	73	I	L. hemicolectomy	250	10.0	0.35	111	34	Yes	
12	F	78	51	III	Sigmoid colectomy	100	3.0	0.1	108	5	Yes	Glycopyrrolate 0.6 mg and neostigmine 2.5 mg antagonism
13	F	42	65	I	Hysterectomy	250	10.0	0.35	65	12	No	
14	F	38	54	I	Hysterectomy	300	8.0	0.25	79	13	No	Atracurium 5 mg for hiccup
15	F	35	65	II	Adrenalectomy	300	7.5	0.35	85	11	Yes	

RESULTS

Intubating conditions were found to be "excellent" or "satisfactory" in all patients. Abdominal relaxation, as assessed by the surgeon, was satisfactory in 13 patients. Two patients received one additional bolus of atracurium (table I) following the surgeon's request for additional relaxation.

Response to nerve stimulation during the infusion was variable: reduction in train-of-four response was seen in all patients, but varied from loss of the fourth twitch to complete abolition of the twitch response.

After skin closure all patients were re-tested with the nerve stimulator. Fourteen patients showed a normal response with no apparent reduction in train-of-four and no fade to tetanic stimulation. One patient (in whom abdominal closure had been completed in 5 min) showed fade and was given neostigmine 2.5 mg plus glycopyrrolate 0.6 mg. All patients appeared normal in the recovery room and none manifested any clinical signs of residual neuromuscular blockade. Hypotension, or cutaneous reactions, suggestive of histamine release were not observed in any patient.

DISCUSSION

Recovery of neuromuscular function following the administration of atracurium is rapid and predictable (Hughes and Payne, 1983). Once the response to transcutaneous nerve stimulation starts to recover, it does so as rapidly as with vecuronium, but with a more favourable T1:T4 ratio (Foldes et al., 1983). These features suggest that it may be safe to dispense with the routine use of an anticholinesterase.

Abdominal closure often requires more muscle relaxation than any other part of a laparotomy. Rapid and predictable recovery from atracurium-induced blockade permits the provision of suitable conditions for closure, whilst reducing the need for antagonism. Neostigmine may have an adverse effect on bowel anastomosis in some patients (Bell and Lewis, 1968); this risk can now be reduced.

In contrast with other neuromuscular blocking agents, the maintenance of paralysis by intermittent bolus injections of atracurium is often unsatisfactory. Rapid recovery of neuromuscular transmission permits little leeway in the timing of repeat doses. This problem may be avoided by the use of a continuous infusion.

Hofmann degradation is largely indepedent of dosage; an infusion of atracurium is, therefore, unlikely to lead to cumulation and prolonged paralysis.

If an infusion technique is to be practicable it must be simple and reliable. Atracurium may be infused undiluted, but this necessitates very fine control of the delivery and tends to waste drug. A solution of atracurium diluted with isotonic saline is stable at room temperature for many hours (Manufacturer's Information) and does not need to be protected from light.

As the degradation of a solution of atracurium is temperature- and pH-dependent it seems possible that it may be adversely affected by mixture with blood and any other i.v. fluid administered during surgery. No such problems were observed during this study and the use of a separate site of venous infusion does not seem justified.

In this study a period of 10 min was allowed before commencing the continuous infusion. This gap was introduced for practical rather than pharmacokinetic reasons, as it allowed time for the establishment of an i.v. infusion and transfer of the patient from the anaesthetic room into the operating theatre. Earlier commencement of the continuous infusion or a faster dose rate (0.4 or 0.5 mg kg^{-1} h^{-1}) might have avoided the need for "top-up" boluses in two patients. In this study only one patient required antagonism of neuromuscular blockade; if more blocker had been used, it is likely that the antagonism of residual blockade would have been necessary in more of the patients.

A study of the dose–response relationship of atracurium in children (Brandom et al., 1985) demonstrated that 0.56 mg kg^{-1} h^{-1} is required to maintain 95% neuromuscular blockade with balanced anaesthesia. This degree of blockade may, however, be in excess of that required to provide good operating conditions.

Some of the patients in this study received 0.6% enflurane (inspired concentration) for short periods. Enflurane and nitrous oxide anaesthesia (to a stable end-tidal enflurane concentration of 0.65 MAC) have been shown to have little effect on the potency of atracurium (Rupp, McChristian and Miller, 1985); it seems unlikely, therefore, that the small amount of enflurane used in this study significantly influenced the results.

Sophisticated neuromuscular monitoring equipment is now available. A variable dose regimen allied to accurate measurement of T1:T4 ratio might produce more consistent results, but would require more complex equipment. The infusion of atracurium has been described previously in association with sophisticated monitoring equipment (Eagar, Flynn and Hughes, 1984; Brandom et al., 1985). This study demonstrates that a standardized regimen used with a basic nerve stimulator can give satisfactory results in most patients. The addition of accurate T1:T4 ratio measurement might permit this technique to be extended to patients with severe metabolic or circulatory derangement.

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DIFFERENTIAL ACTIONS OF VOLATILE ANAESTHETIC AGENTS ON A SINGLE ISOLATED NEURONE

G. A. WESTON AND S. H. ROTH

SUMMARY

The precise mechanism(s) and site(s) of action of general anaesthetic agents remain a mystery. The early theories of anaesthesia concentrated on a unitary mechanism; however, many recent investigations emphasize specific interactions between anaesthetic agents and excitable membranes. In this study volatile anaesthetics (halothane, isoflurane, enflurane and diethyl ether) applied as vapours in clinical concentrations were observed to produce differential effects on the discharge activity of an isolated crayfish neurone. In addition, both enflurane and diethyl ether induced bursts of discharge activity at concentrations known to produce EEG seizure activity in animals and man. These observations do not support the concept of a common non-specific mechanism of action, but provide further evidence that the action of volatile anaesthetics is selective and may involve multiple sites or mechanisms, or both.

The first demonstration of general anaesthesia using diethyl ether marked the beginning of an era in which the administration of volatile hydrocarbons has become a major component of general anaesthesia. In recent years, halogenated agents such as halothane, isoflurane and enflurane have been introduced, but despite extensive research little is known of their mechanism(s) and sites of action.

Early theories of anaesthesia supported the concept of a unitary mechanism of action (Roth, 1979; Roth, 1980a; Norman, 1983), and emphasized the importance of lipid solubility. It has been well documented that anaesthetic potency correlates well with lipid solubility, and the chemical and structural diversity of active agents lends support to a non-specific interaction and common molecular mechanism (Ueda and Kamaya, 1984).

There is considerable evidence, however, which supports multiple mechanisms or sites of action, or both (Richards et al., 1978; Franks and Lieb, 1982; Labella, 1982; Haydon and Urban, 1983; Richards, 1983). Selectivity of action, which occurs in both the intact organism and isolated tissues (Judge, 1983; Miller and Pang, 1976; Roth, 1980b; Shimoji, Fujioka and Ebata, 1984), suggests that there may be specific interactions and unique mechanisms which differ for each anaesthetic agent (Roth, 1980c; Franks and Lieb, 1984). The question remains whether such selectivity occurs at the level of the single neurone. The objective of this study was to determine whether the volatile anaesthetics diethyl ether, halothane, enflurane and its structural isomer, isoflurane, produce differential effects on the activity of a single isolated neurone.

MATERIALS AND METHODS

The isolated single neurone preparation used for this study was the muscle receptor organ or stretch receptor from the second or third abdominal segment of the crayfish (*Procambaris clarkii*). Neurones and receptor muscle fibres were dissected with a length (5–10 mm) of dorsal nerve and placed in a small glass tissue chamber mounted in a glass water jacket cooled by a circulating pump (Roth, 1980b). Each end of the group of muscle fibres was clamped firmly by a pair of fine forceps mounted on micromanipulators. The forceps were

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Gerald A. Weston, m.b., ch.b., f.f.a.r.c.s. (Department of Anaesthesia); Sheldon H. Roth, b.sc., m.sc., ph.d. (Departments of Anaesthesia, and Pharmacology and Therapeutics); Faculty of Medicine, The University of Calgary, 3330 Hospital Drive, N.W. Calgary, Alberta T2N 4N1, Canada.

Correspondence to S.H.R., Department of Pharmacology and Therapeutics.

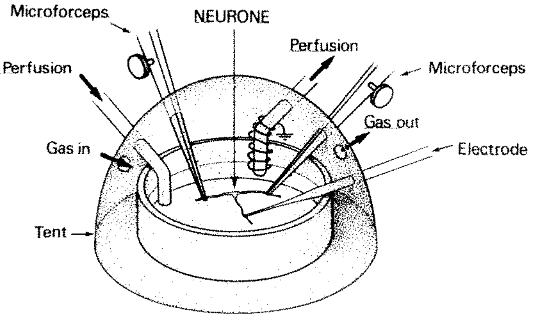

FIG. 1. A schematic diagram of the tissue chamber and apparatus enclosed in a tent of plastic film. Oxygen flow through the tent was maintained at 3 litre min^{-1} (gas in/gas out). Anaesthetic vapour was added to the oxygen flow using calibrated vaporizers (not shown). The tissue chamber with mounted neurone was continuously perfused with physiological solution at a flow rate of 3 ml min^{-1}.

positioned to produce a desired tension in the muscle fibres, thus generating a controlled discharge frequency of action potentials in the neurone. The tissue chamber was perfused continuously with pre-cooled modified Van Harrevelds (Van H) solution (Van-Harreveld, 1936) at a flow rate of 3 ml min^{-1}. The temperature of the bathing medium was 10 ± 1 °C, monitored by a thermistor probe, and the pH of all solutions was 7.2. The volume of the chamber was approximately 1.5 ml and was kept constant by a fixed level aspirator (fig. 1).

Extracellular action potentials at a maintained stimulus (stretch) were recorded from the dorsal nerve using a glass suction electrode near the cut end of the nerve. Electrical signals were amplified (Grass P15B preamplifier) and displayed on a storage oscilloscope. The discharge frequency was analysed using a microprocessor frequency counter, and frequency–time histograms were generated and displayed on a chart pen recorder.

Previously, it had been observed (Roth and MacIver, 1979) that a suitable maintained tension produced an initial rapid discharge (20–30 Hz) which decayed slowly to a plateau of approximately 5 Hz. This basal level of rhythmical firing continued for several hours and provided an ideal baseline for the examination of the effects of the volatile anaesthetics on neuronal activity.

The complete tissue chamber was enclosed in a "tent" of plastic film (fig. 1) and a continuous flow (3 litre min^{-1}) of 100% oxygen was delivered into the tent from a standard Boyle anaesthetic machine. A period of 1 h was allowed for stabilization before the administration of the anaesthetic vapours.

Volatile anaesthetic agents were supplied, by addition to the oxygen flow, from calibrated vaporizers (Ohio Medical Products, Ontario, Canada) for isoflurane and enflurane and a Fluotec Mark 2 (Cyprane Ltd, England) for halothane. A Copper Kettle (Fraser Sweatman Inc., Hatfield P.A.) was used for diethyl ether and the higher concentrations of halothane (greater than 4 vol%). Concentrations of the anaesthetic vapours are indicated as volume percent (vol%) and refer to settings on the dial of the calibrated vaporizers, or were selected by adjusting the oxygen flow rate through the Copper Kettle. Accurate measurements of anaesthetic concentrations in the aqueous medium bathing the neurone were determined using a Hewlett–Packard gas chromatograph (5880 A) fitted with a glass column packed with Poropak Q. Nitrogen was used as the carrier gas at a flow rate of 40 ml min^{-1}. The temperatures of the oven, injector and flame ionization detector were 130 °C, 150 °C and 190 °C, respectively. Test samples were taken from the tissue chamber with a 10-μl gas-tight Hamilton syringe and injected directly to the column. Peak area values were plotted against known concentrations of standards prepared in gas-tight vials. This procedure permitted the calculation of the aqueous concentrations in the bath.

A single neurone was exposed to only one agent, in stepwise increments of concentration to generate concentration–response curves. Each concentration of anaesthetic vapour was applied for approximately 10 min followed by a recovery period of at least 10 min with a maintained flow of oxygen. The changes in discharge activity in the presence of anaesthetic agent and during recovery were calculated as a percentage of the control (pre-drug) values.

The modified control physiological Van H solution contained (mmol litre^{-1}): NaCl 205; KCl 5.4; $CaCl_2$ 13.5; $MgCl_2$ 2.6; and Trizma (Tris(hydroxy-methyl) aminomethane) 10. Halothane B.P. was obtained from Halocarbon (Ontario) Ltd, isoflurane and enflurane from Ohio Medical Anaesthetics, Quebec, Canada and diethyl ether from Fisher Scientific, Edmonton, Canada.

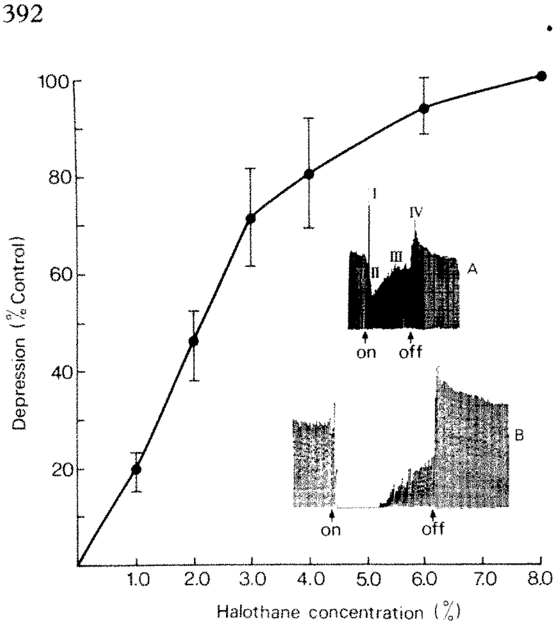

FIG. 2. The effects of halothane vapour on the discharge activity of the sensory neurone are concentration- and time-dependent. The maximum depression of discharge rate as % control is plotted against halothane vapour concentrations as indicated on the dial of the vaporizer. Each point is the mean ± SEM of five neurones. The frequency–time histograms at an ED_{50} (inset A) and higher concentration (inset B) show the time-dependent profile of effects that occur on exposure (on) and during washout (off). Each bin of the histogram represents a sampling time of 10 s. The control rate of firing was approximately 5 Hz.

RESULTS

In general, all the anaesthetic vapours examined produced concentration- and time-dependent alterations of the stretch-induced discharge activity of the sensory neurone. Although there was some degree of similarity in response, each anaesthetic displayed a characteristic profile of effects. The dominant effect for all the volatile anaesthetics was a concentration-dependent depression of discharge rate. The distinct differences between the volatile agents studied are described separately. The onset of response to an effective concentration of vapour was immediate, usually within seconds of setting the dial on the vaporizer. The reversal or *off* response, that is washout, was equally rapid.

Halothane

We chose halothane as a prototype to describe the phases of the time-dependent alterations in discharge activity because, on initial exposure to vapour concentrations in the range of 1–8 vol %, this agent produced an immediate, but transient, enhancement in firing rate in addition to the subsequent responses produced by the other agents. This initial period of enhancement was termed phase I (fig. 2A). Continued exposure of the neurone to halothane resulted in a subsequent, concentration-dependent, decrease in discharge rate until, at concentrations approaching 6 vol %, total depression was observed (fig. 2B). This depressant phase was termed phase II (fig. 2A), and occurred within 30 s of phase I. In the continued presence of halothane vapour, within a 5-min period, there was partial recovery of the attenuated rate of discharge. This response was termed phase III (fig. 2A). Withdrawal of the halothane from the oxygen flow resulted in an immediate increase in discharge activity to values greater than control. This reversal, or washout enhancement, lasted for approximately 5 min before values returned to control, and was termed phase IV (fig. 2A).

Isoflurane

The effects of isoflurane in the concentration range 1–5 vol % were similar to those of halothane with the exception that this agent did not produce excitation (phase I). Isoflurane produced an initial concentration-dependent decrease in discharge rate—within 1 min of the start of the administration. At concentrations approaching 4–5 vol %, total depression was produced (fig. 3, inset). Partial recovery of discharge rate followed the depressant phase in the continued presence of isoflurane. At the end of the period of administration an immediate increase in discharge rate to values faster than control was also observed with subsequent return to control values (fig. 3, inset). Thus, in comparison with halothane, isoflurane did not produce phase I, but did exhibit similar responses during phases II, III and IV.

Enflurane

This agent is a structural isomer of isoflurane and at applied concentrations below 3.5 vol % produced a response profile similar to that of isoflurane (fig. 4A). However, at concentrations of enflurane greater than 3.5 vol %, irregular bursts of firing activity were produced which persisted until the cessation of administration (fig. 4B, C). This effect was also observed during phase I before the total depression of firing activity. When the enflurane vapour was discontinued, the

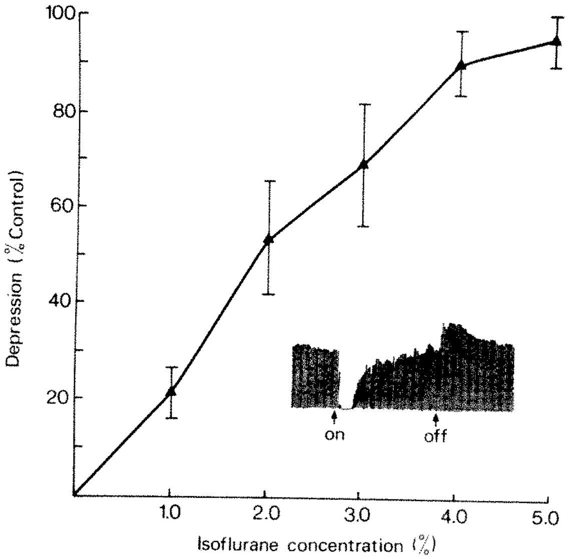

FIG. 3. Concentration–response curve for isoflurane. Each point represents the mean ± SEM of five determinations. An example of a frequency–time histogram is shown in the inset. Bin width of histogram is 10 s, and control firing rate is approximately 5 Hz.

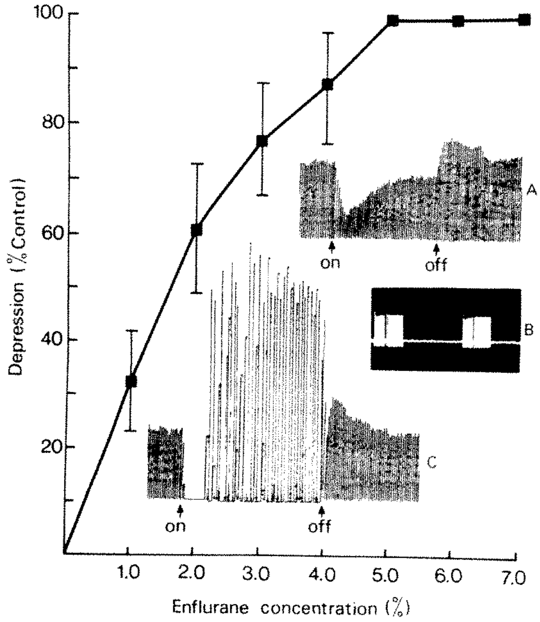

FIG. 4. Enflurane produces a concentration-dependent depression of discharge activity of the sensory neurone. Inset (A) shows the time-dependent profile of effects at concentrations less than 3.5 vol %. At concentrations greater than 3.5 vol %, burst discharges occur, shown on the oscillograph (inset B), and frequency–time histogram (inset C). Characteristics of histograms are similar to those of figure 2.

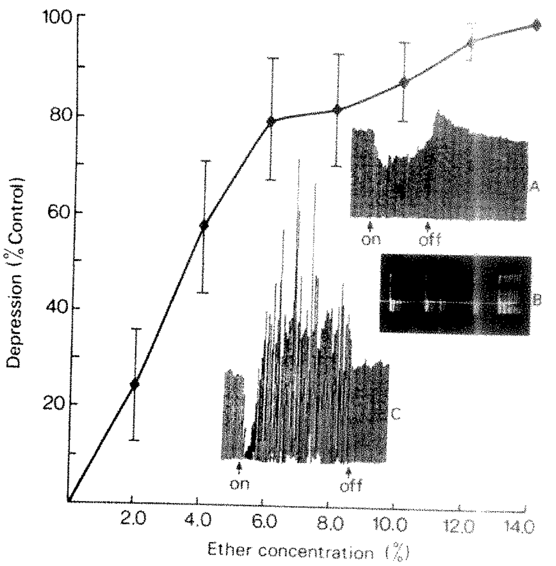

FIG. 5. The frequency time histogram (inset A) for diethyl ether is similar to that for enflurane. At concentrations of 8 vol % or greater, ether produces burst activity of very irregular patterns (oscillograph inset B, frequency–time histogram inset C). Characteristics of histograms are similar to those of figure 2.

discharge activity returned to a control rhythmical pattern within 1 min, but at a value greater than the control rate, before returning—within 5 min—to pre-drug (control) values (phase IV).

Ether

The effects of diethyl ether vapour at concentrations of 2–14 vol % were similar to those of enflurane: that is, at low concentrations (less than 8 vol %) initial depression, recovery and enhancement on washout were observed (fig. 5A). At higher concentrations (greater than 8 vol %) burst activity occurred during phases I and III, and persisted until the end of the period of administration (fig. 5B). Upon discontinuation of the diethyl ether vapour the discharge activity became regular within 1 min. During phase IV, an increase in discharge rate was observed which gradually returned to control over the next 5 min. Thus for enflurane and diethyl ether there was no phase I. At concentrations below 3.5 and 8 vol % respectively, phases II, III and IV were seen but at higher concentrations, phase III (partial recovery) was observed to consist of an irregular firing pattern or burst activity (figs 4B, C, 5B, C). On discontinuation of the agent, an enhanced rate of firing and subsequent return to control were observed (figs 4A, 5A).

DISCUSSION

The sensory neurone or stretch receptor of the crayfish has been used frequently as a model system to study the effects of a variety of pharmacological agents. In previous studies it has been shown that this neurone is capable of discriminating the structural differences between anaesthetics (Roth and Omand, 1982), barbiturates (Aickin and Deisz, 1981; Roth, Tan and Tooth, 1983) and benzodiazepines (Sewell, Tan and Roth, 1984a; Tan, Sewell and Roth, 1984). These observations provide support for selective non-receptor interactions of various drug molecules with neuronal membranes (Sewell, Tan and Roth, 1984b). In this study we have demonstrated that this single isolated neurone is also capable of responding in a differential manner to volatile anaesthetics. These agents produced not only concentration-dependent effects, but also graded time-dependent alterations in activity which may reflect differential kinetics at the cellular or membrane level.

Frequency–time histograms were useful to demonstrate the differential responses. Although all the agents produced depression of firing activity during phase II, marked differences occurred in phases I and III. The differences may be regarded as subtle, but bear some similarity to the responses which occur in the intact organism, and do suggest that the interaction of volatile anaesthetics with neuronal membranes is far more complex than could be explained by a simple mechanism of lipid solubility.

It is interesting to note that the vapour concentrations of enflurane and diethyl ether that produced burst activity in this preparation are known to be associated with EEG seizure activity in man (Neigh, Garman and Harp, 1971) and animals (Julien and Kavan, 1972; Burcheil, Myers et al., 1975; Burcheil, Stockard et al., 1975; Winters, 1976; Stevens et al., 1984). Seizures associated with ether were first reported by Pinson (1927). *In vivo*, halothane and isoflurane do not produce abnormal EEG activity (Joas, Stevens and Eger, 1971), and this is compatible with our data. Enflurane and ether also produce excitatory seizure-like activity in hippocampal cells of brain slice preparations (Richards and White, 1975; MacIver, Harris and Roth, 1984) and in some cells in the olfactory cortex (Richards, Russell and Smaje, 1975).

TABLE I. *Effective concentrations for halothane, isoflurane, enflurane and diethyl ether on the sensory neurone and calculated membrane concentrations at equi-effective aqueous values. *From dose–response curves*

Agent	Concentrations measured in tissue chamber (mmol litre^{-1})	ED$_{50}$ for sensory neurone* (mmol litre^{-1})	Calculated membrane concentration (mmol litre^{-1})
Halothane	0.14–0.66	0.26	57.2
Enflurane	0.04–0.5	0.15	18
Ether	18–117	32.5	104
Isoflurane	0.1–0.475	0.275	32.7

As described above, aliquots of perfusate were sampled during periods of administration and the ranges of the concentrations measured are shown in table I. The concentrations required to depress the discharge activity by 50% of control (ED$_{50}$) were determined from the dose–response curves (table I). Multiplying the ED$_{50}$ concentrations by the appropriate oil/water partition coefficients (Steward et al., 1973; Atkinson, Rushman and Lee, 1982; Brown, Blitt and Vaughan, 1985) resulted in estimates of the membrane concentrations at equi-effective concentrations. The membrane concentrations are only approximate; neither the oil/water partition coefficient nor membrane buffer partition coefficients are a true value of the partition coefficient for the invertebrate neurone; however, it is interesting that the mean value of the estimated membrane concentrations is approximately 53 mmol/litre of membrane (oil), which agrees very well with the predicted value (50 mmol litre^{-1}) in the early reports of the lipid theories of anaesthesia (Seeman, 1972). Thus, the rule holds true: that is a critical concentration of anaesthetic appears to be attained in the membrane phase in association with anaesthesia. What cannot be explained by this rule are the differential effects on discharge activity of the neurone in response to the applied agents (see also Landau, Richter and Cohen, 1979).

In vivo, many anaesthetics exhibit characteristic pharmacological profiles of activity that include biphasic responses of depression and activation (Stevens et al., 1984). There is no intent to extend the results of this study on a single neurone to explain those effects observed in the intact organism. However it is feasible that, if similar effects occur in the central nervous system, it is highly probable that anaesthesia is not a simple state associated with only depression, but may involve rather complex alterations of neuronal discharge (Winters, 1982). We have demonstrated differential effects of volatile anaesthetics at the neuronal level, and propose that "recognition" sites exist in the membrane phase for anaesthetics or the structural complexity of the membrane phase would create discrete subregions sensitive to the structure of the anaesthetic (Halsey, 1984).

ACKNOWLEDGEMENTS

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EFFECTS OF TUBOCURARINE ON PLASMA HISTAMINE CONCENTRATION IN THE RAT

Correlation with the Release of Histamine from Isolated Mast Cells

Y. KUBOTA

SUMMARY

The administration of tubocurarine i.v. in man produces hypotension, probably as a result of the release of histamine. The mechanisms involved in this action of tubocurarine on the plasma histamine concentration in rats, and on the isolated peritoneal mast cells were investigated. I.v. injections of tubocurarine (> 5 mg kg^{-1}; corresponds to tubocurarine 4×10^{-4} mol litre^{-1} in the plasma of the rats) evoked a phasic increase in plasma histamine concentration. In vitro *studies showed that tubocurarine 4×10^{-4} mol litre^{-1} released about 20% of the histamine contained in the isolated mast cells. Treatment of the mast cells with carbachol or atropine evoked no histamine release, nor did it modify the tubocurarine-induced release of histamine. These results suggest that the increased histamine concentrations in the plasma are attributable to an action of tubocurarine on the mast cells which is not mediated through the acetylcholine receptors distributed on these cells.*

Recent radioenzymatic investigations of plasma histamine concentration in man following the administration of tubocurarine suggest that the release of histamine is an important factor in the genesis of the hypotension which accompanies the administration of tubocurarine, as the hypotension is temporally and quantitatively related to the absolute plasma histamine concentration (Moss et al., 1981). However, little is known of the mechanisms involved. In an attempt at elucidation, we have observed the effects of tubocurarine on the plasma histamine concentration in anaesthetized rats. In addition, peritoneal mast cells were isolated and used to investigate the cellular mechanisms involved in the release of the histamine.

MATERIALS AND METHODS

Male W.K.A. rats (300 ± 10 g) were anaesthetized with ether, and their lungs ventilated artificially (Harvard; 70 b.p.m., volume 2 ml/breath). Heparinized catheters (27-gauge) were inserted to a femoral vein for administration of tubocurarine and to the contralateral femoral artery to permit the collection of blood. Blood samples (0.8 ml) were collected, 1, 5, 10, 15, 20 and 30 min after the injection of the test substance, into heparinized plastic syringes, then transferred immediately to non-heparinized ice-cold plastic tubes and centrifuged at 10000 *g* for 20 min at 4 °C. The plasma fraction was carefully collected, and stored at −20 °C until assayed.

Peritoneal mast cells were obtained from male W.K.A. rats (250–350 g) according to Saeki (1964). The mixed peritoneal cells containing about 8% mast cells were purified by differential centrifugation through bovine serum albumin (BSA) (37% w/v) to contain approximately 80% mast cells, and were suspended in modified Krebs solution (composition mmol litre^{-1}: NaCl 142, KCl 4.7, $MgSO_4$ 1.2, $CaCl_2$ 1.0, Na_2HPO_4 2.5, KH_2PO_4 0.6, glucose 5.6) containing bovine serum albumin 0.5 mg ml^{-1}.

The mast cells were washed twice with ice-cold modified Krebs solution and re-suspended (1×10^6 mast cells ml^{-1}) in the same solution and were kept in an ice-box, except during incubation.

YASUTAKA KUBOTA, Department of Pharmacology, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan. Present address: Department of Oral Surgery, Faculty of Dentistry, Kyushu University, Fukuoka 812, Japan.

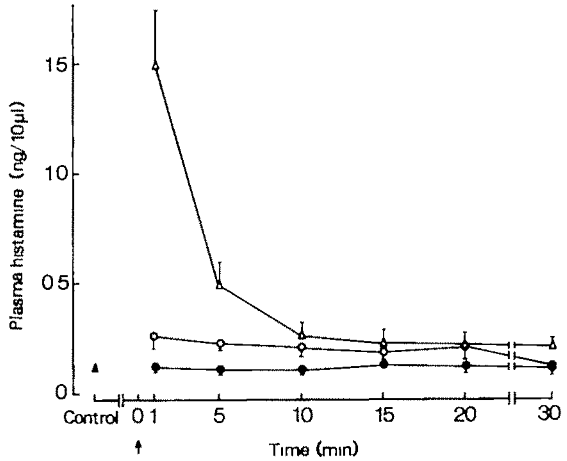

FIG. 1. Effects of i.v. injection of tubocurarine on plasma histamine concentrations in anaesthetized rats. The control plasma histamine concentration was 0.12±0.01 ng/10 µl (▲) ($n = 19$). Saline(●), tubocurarine 5 mg kg^{-1} (○) or tubocurarine 10 mg kg^{-1} (△) was injected to the femoral vein at the time zero indicated by the arrow. Blood samples (0.8 ml) were collected from the femoral artery at various times after the injection. Each point with vertical bars indicates the mean ± SEM values of three to six experiments.

Ca^{2+}-free solution was prepared by omitting Ca^{2+} and adding ethyleneglycol-bis-N,N′-tetra-acetic acid (EGTA), and high Ca^{2+} solution was prepared by adding Ca^{2+} in the presence of N-2-hydroxyethyl-piperazine-N′-2-ethanesulphonic acid (HEPES) instead of phosphate buffer system. The pH of all solutions was adjusted to 7.2 before use.

To observe the effects of tubocurarine, mast cells were incubated for 10 min with various concentrations of tubocurarine at 37 °C and the reaction was terminated by placing the tubes in an ice-box. To study the effects of carbachol or atropine, mast cells were preincubated with these agents for 5 min at 37 °C and then incubated, with or without tubocurarine, for 10 min at 37 °C.

Histamine was assayed by a fluorometric method, using high pressure liquid chromatography (HPLC) (Tsuruta, Kohashi and Ohkura, 1978; Kubo, Oka and Frey, 1981). None of the drugs used in the present study interfered with the fluorometric assay. Histamine secretion from isolated mast cells (supernatant histamine) was expressed as the percentage of total cell histamine (cellular and supernatant) or as a percentage of maximum histamine secretion. Values are expressed as the mean ± SEM.

The following chemicals were used: tubocurarine chloride (Sigma Chemical Co., St Louis, Mo, U.S.A.); atropine sulphate (Merck, Darmstadt, FRG); carbachol (Tokyo Kasei, Tokyo, Japan); EGTA, HEPES (Dozin, Kumamoto, Japan).

RESULTS

Effects of tubocurarine on plasma histamine concentration

The plasma histamine concentration in the anaesthetized rats ranged from 0.05 to 0.22 ng/10 µl, giving a mean value of 0.12±0.01 ng/10 µl ($n = 19$). With the injection of tubocurarine > 5 mg kg^{-1} i.v., plasma histamine concentrations showed phasic increases with the peak value being observed 1 min after the injection of tubocurarine. Figure 1 shows the time-course of the plasma histamine concentration after the injection of tubocurarine. The means of the peak values were 0.26±0.06 and 1.50±0.26 ng/10 µl, when 5 and 10 mg kg^{-1} of tubocurarine were administered, respectively.

Effects of tubocurarine on the isolated mast cells

In an attempt to obtain a clue as to the mechanism(s) involved in the increase in histamine concentration associated with the administration of tubocurarine, peritoneal mast cells were isolated and the effects of tubocurarine on the mast cells were investigated.

Mast cells viewed by phase contrast microscopy are highly reflectile, and have regular outlines (Cochrane and Douglas, 1974). The cells exposed to tubocurarine > 3×10^{-4} mol litre^{-1} at room temperature became swollen, showed irregular outlines and were finally surrounded by extruded granules, indicating bubbling secretory responses.

The histamine released from the isolated mast cells by tubocurarine > 1×10^{-4} mol litre^{-1} was assayed using a fluorometric method with HPLC. The amount of histamine released increased in a dose-dependent manner; the maximum value was obtained at tubocurarine 3×10^{-3} mol litre^{-1} (fig. 2). The amount of histamine released by tubocurarine 3×10^{-3} mol litre^{-1} was in the range 1.27–1.34 ng per 10^5 mast cells, and was 66.3±3.8% of the total histamine contained in the isolated mast cells.

Effects of Ca^{2+} on the action of tubocurarine

Calcium ions play a key role in the stimulus–secretion coupling in mast cells (Douglas, 1968),

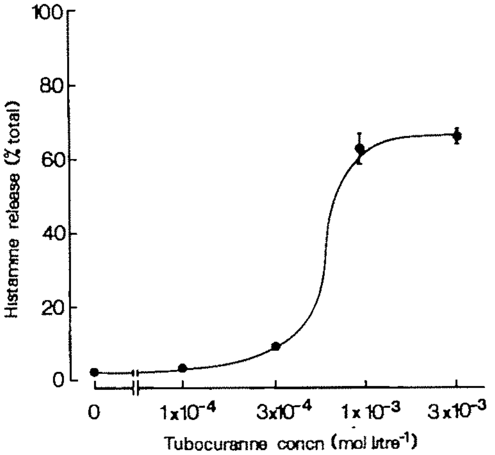

FIG. 2. Effects of tubocurarine 1×10^{-4}–3×10^{-3} mol litre^{-1} on isolated mast cells. Isolated mast cells were incubated with tubocurarine for 10 min at 37 °C. Tubocurarine $> 3 \times 10^{-4}$ mol litre^{-1} released histamine from the isolated mast cells, and the amount of released histamine (supernatant histamine) was expressed as the percentage of total cell histamine (cellular and supernatant). Spontaneous histamine release was 2.4%. Closed circles with vertical bars indicate the mean ± SEM values of four experiments.

and the direct injection of Ca^{2+} to mast cells through a micropipette initiates the release of histamine (Kanno, Cochrane and Douglas, 1973). Therefore, we observed the effects of Ca^{2+} on the release of histamine from mast cells produced by tubocurarine.

Figure 3A shows the effects of Ca^{2+}-free solution on the tubocurarine-induced histamine release from mast cells. When mast cells were incubated with a Ca^{2+}-free solution containing EGTA 1 mmol litre^{-1}, tubocurarine $> 3 \times 10^{-4}$ mol litre^{-1} evoked a discrete histamine release, and there was no difference in the amount of histamine released by a relatively low concentration of tubocurarine (3×10^{-4} mol litre^{-1}) in the presence or absence of Ca^{2+}. However, when relatively high concentrations of tubocurarine (10^{-3} or 3×10^{-3} mol litre^{-1}) were applied, the amount of histamine released was 32.9 or 42.4% of the control values in the Ca^{2+}-free solution containing EGTA. Therefore, the mast cells were treated with a solution containing Ca^{2+}-free EGTA 2 mmol litre^{-1} for 1 h at 37 °C, and then the effects of various concentrations of tubocurarine were observed in the presence of a Ca^{2+}-free solution containing EGTA 1 mmol litre^{-1}. As shown in figure 3A, tubocurarine 3×10^{-4} or 10^{-3} mol litre^{-1} did not induce a release of histamine but, at

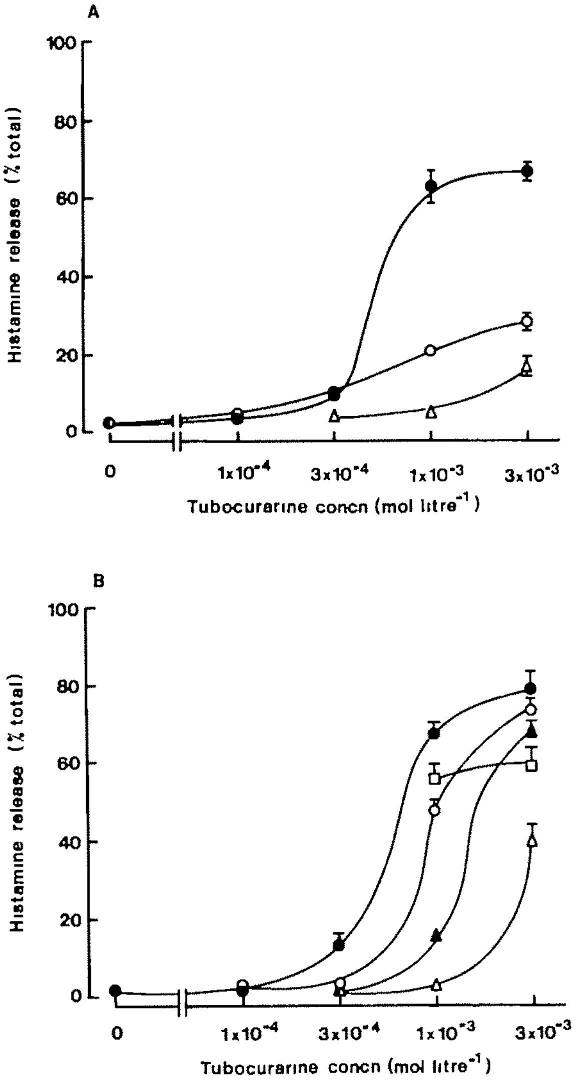

FIG. 3. Effects of various concentrations of $[Ca^{2+}]_o$ on the tubocurarine 1×10^{-3} mol litre^{-1}-induced histamine release. A: Effects of Ca^{2+}-free solution on the tubocurarine-induced histamine release. Isolated mast cells were incubated with tubocurarine for 10 min at 37 °C in the presence of Ca^{2+} 1 mmol litre^{-1} (●) (control) or in a Ca^{2+}-free Krebs solution containing EGTA 1 mmol litre^{-1} (○). To observe the effects of Ca^{2+}, isolated mast cells were preincubated with a Ca^{2+}-free Krebs solution containing EGTA 2 mmol litre^{-1} for 1 h at 37 °C, and then incubated with tubocurarine for 10 min at 37 °C in a Ca^{2+}-free Krebs solution containing EGTA 1 mmol litre^{-1} (△). B: Isolated mast cells were incubated with tubocurarine for 10 min at 37 °C in HEPES buffer solution in the presence of various concentrations of Ca^{2+}: 0.1 mmol litre^{-1} (□); 1 mmol litre^{-1} (●); 2 mmol litre^{-1} (○); 5 mmol litre^{-1} (▲) or 10 mmol litre^{-1} (△). Spontaneous histamine release was less than 2.9% and was not affected by $[Ca^{2+}]_o$. Each point indicates the mean ± SEM values of three to five experiments.

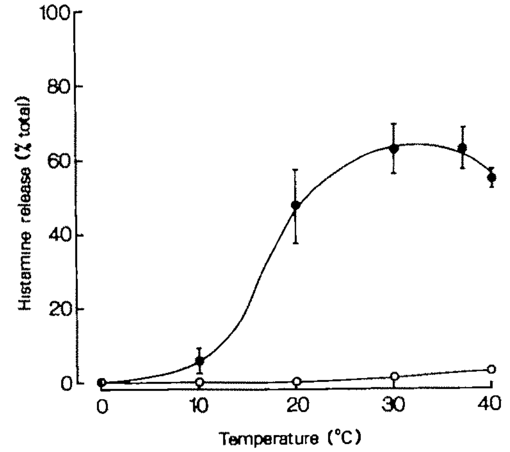

FIG. 4. Effects of temperature on histamine release induced by tubocurarine 1×10^{-3} mol litre^{-1}. Isolated mast cells were incubated at each temperature for 10 min with tubocurarine (●) or without tubocurarine (○). Each point indicates the mean ± SEM values of three experiments.

3×10^{-3} mol litre^{-1}, this agent evoked a minute but discrete histamine release (25.5% of the control value). These results indicate that the Ca^{2+} required for the tubocurarine-induced release of histamine from mast cells is mainly of extracellular origin, and that Ca^{2+} stored in the cell is utilized only when a high concentration of tubocurarine (3×10^{-3} mol litre^{-1}) is applied.

Figure 3B shows the effects of stepwise increases in Ca^{2+} concentrations (0.1–10 mmol litre^{-1}) on the tubocurarine-induced release of histamine. Increase in concentrations of Ca^{2+} (1–10 mmol litre^{-1}) suppressed the tubocurarine-induced release of histamine in a concentration-dependent manner: the amount of histamine released by tubocurarine 3×10^{-4}–3×10^{-3} mol litre^{-1} was decreased to 27.9–93.0 or 11.5–86.9% of the control value in the presence of Ca^{2+} 2 or 5 mmol litre^{-1}, respectively.

Furthermore, in the presence of Ca^{2+} 10 mmol litre^{-1}, relatively low concentrations of tubocurarine (3×10^{-4} or 10^{-3} mol litre^{-1}) did not evoke a release of histamine, although at 3×10^{-3} mol litre^{-1}, this agent released histamine (50.4% of the control value). The antagonism between tubocurarine and $Ca^{2+} > 1$ mmol litre^{-1} was non-competitive in nature.

Stepwise decrease in extracellular Ca^{2+} concentrations in the range 1.0–0.1 mmol litre^{-1} also led to a reduction in the amount of histamine released by tubocurarine, thereby indicating that the tubocurarine-induced release of histamine occurs preferentially at the concentration of Ca^{2+} 1 mmol litre^{-1}. Therefore, Ca^{2+} has dual effects — the facilitatory and inhibitory effects on the tubocurarine-induced release of histamine from mast cells.

Effects of temperature on the tubocurarine-induced histamine release

Figure 4 shows the effects of temperature on the tubocurarine-induced release of histamine from mast cells. The maximum release of histamine was observed between 30 and 37 °C. At temperatures ranging between 0 and 30 °C, the tubocurarine-induced histamine release increased, in a temperature-dependent manner. The Q_{10} value was 2.38 (0–20 °C).

Effects of carbachol and atropine on the action of tubocurarine

To investigate whether or not the tubocurarine-induced histamine release correlates with the nicotinic or muscarinic acetylcholine receptors distributed on the mast cells, the effects of carbachol and atropine were observed. As shown in figure 5, application of either carbachol 10^{-7}–10^{-4} mol litre^{-1} or atropine 10^{-5}–10^{-4} mol litre^{-1} did not evoke a release of histamine from the mast cells. Furthermore, the tubocurarine-induced release of histamine was not affected by the presence of carbachol 10^{-7}–10^{-4} mol litre^{-1} or atropine 10^{-5}–10^{-4} mol litre^{-1}, thereby indicating that nicotinic and muscarinic acetylcholine receptors are not involved.

DISCUSSION

The present results confirmed previous observations that i.v. injections of tubocurarine increase the plasma histamine concentration in various species, including man (Mongar and Whelan, 1953; Moss et al., 1981). In the present studies, the increase in the plasma histamine concentration induced in the rat by tubocurarine was observed with doses greater than 5 mg kg^{-1}, and this dose roughly corresponds to the concentration of tubocurarine 4×10^{-4} mol litre^{-1} in the plasma of the anaesthetized rats. *In vitro* experiments indicated that tubocurarine 4×10^{-4} mol litre^{-1} releases about 20% of the total histamine contained in the isolated mast cells (fig. 1). Thus, the present results suggest that tubocurarine injected to the animals releases histamine from

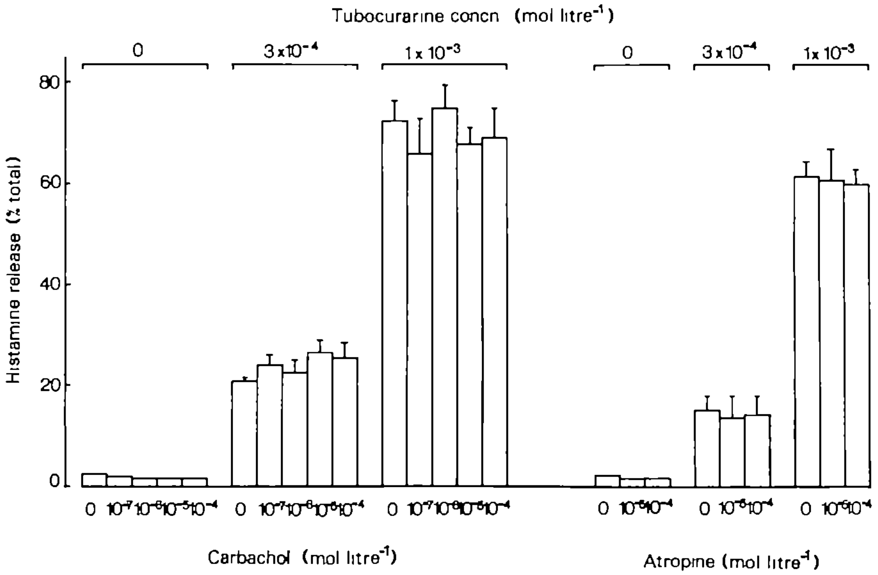

FIG. 5. Effects of carbachol or atropine on the release of histamine from mast cells and the tubocurarine-induced histamine release. Isolated mast cells were preincubated with carbachol or atropine for 5 min at 37 °C and then incubated with or without tubocurarine for 10 min at 37 °C. Each value is the mean ± SEM values of three to six experiments.

mast cells distributed in various tissues, basophils or extracellular fluid and so increases the plasma histamine concentration.

The secretory response of the mast cells requires Ca^{2+}, as is the case with other exocytotic secretory responses (Douglas, 1968; Rubin, 1970). The release of histamine from mast cells induced by an antigen–antibody reaction on the cell membrane (Mongar and Schild, 1958; Foreman and Mongar, 1972), neurotensin (Carraway et al., 1982), compound 48/80 (Cochrane and Douglas, 1974; Cochrane et al., 1982) or by dynorphin-(1–13) (Sugiyama and Furuta, 1984) are dependent on the presence of intra- or extra-cellular Ca^{2+}. It appears that an influx of Ca^{2+} from the extracellular environment to the mast cells is a sufficient stimulus to initiate histamine secretion. Such an influx of Ca^{2+} may be produced experimentally with calcium ionophore, A23187 (Foreman, Mongar and Gomperts, 1973; Foreman, Hallett and Mongar, 1977) or by the injection of calcium to mast cells (Kanno, Cochrane and Douglas, 1973). However, relatively low concentrations of Ca^{2+} (> 1.5 mmol litre^{-1}) suppressed the histamine release induced by neurotensin (Carraway et al., 1982), compound 48/80 (Cochrane et al., 1982) and by dynorphin-(1–13) (Sugiyama and Furuta, 1984).

In the present studies, the inhibitory action of $[Ca^{2+}]_0 > 2$ mmol litre^{-1} on the secretory response initiated by tubocurarine was also evident. Mast cells incubated in $[Ca^{2+}]_0$ 10 mmol litre^{-1} Krebs solution released only 50.4% of the histamine released in the presence of $[Ca^{2+}]_0$ 1 mmol litre^{-1} in response to tubocurarine 3×10^{-3} mol litre^{-1}. On the other hand, pretreatment of the mast cells with a Ca^{2+}-free solution containing EGTA practically blocked the histamine release by tubocurarine. Thus, Ca^{2+} has dual (facilitatory and inhibitory) effects on the histamine release from mast cells by tubocurarine.

The mechanisms involved in the inhibition by $[Ca^{2+}]_0 > 2$ mmol litre^{-1} on the secretory response are unknown. It may be that Ca^{2+} inhibits the binding of tubocurarine to mast cells, as in the case of neurotensin (Lazarus, Perrin and Brown, 1977), or that Ca^{2+} acts to regulate its own entry or the mobilization of cellular Ca^{2+} within mast cells membrane as reported by Cochrane and colleagues (1982).

Previous observations (Douglas and Ueda, 1973; Cochrane and Douglas, 1974; Diamant and Patkar, 1975) suggested that cell-fixed Ca^{2+} is important for the release of histamine induced by compound 48/80. The present results support this hypothesis, since simply removing the Ca^{2+} from the bathing solution reduced, but did not abolish, the secretory response elicited by tubocurarine. However, tubocurarine 3×10^{-4}–10^{-3} mol litre^{-1} did not release histamine after 1 h of incubation in a Ca^{2+}-free solution containing EGTA.

Carbachol or atropine evoked no histamine release, and neither agent affected the actions of tubocurarine on the histamine release from mast cells. These observations indicate that tubocurarine releases histamine without acting on the acetylcholine receptors distributed on the surface membrane of mast cells.

In contrast, Mannaioni and his coworkers reported that acetylcholine interacts with muscarinic receptors in isolated rat mast cells, causing histamine secretion (Fantozzi et al., 1978; Blandina et al., 1980). Furthermore, acetylcholine was shown to induce histamine secretion only in sensitized rats (Schmutzler, 1978). However, negative results were obtained by other research groups (Kiernan, 1972; Kazimierczak and Diamant, 1978; Kazimierczak, Adamas and Maslinski, 1980), who found no secretory response to acetylcholine in isolated rat mast cells. Moreover, Mannaioni's group also reported that murine neoplastic mast cells did not release histamine when exposed to acetylcholine, and even isolated rat mast cells sometimes did not respond to cholinergic stimulation (Masini et al., 1981). These discrepancies in response to acetylcholine on the histamine release should be clarified by further investigation.

The release of histamine from isolated mast cells is induced not only by neuromuscular blocking drugs, but also by general anaesthetics, narcotics and peptide hormones such as neurotensin or dynorphin (Hainsworth and Bingham, 1970; Vervloet et al., 1979; Carraway et al., 1982; Sugiyama and Furata, 1984). Furthermore, in the case of dynorphin-(1–13), a synthetic dynorphin which is a potent opioid peptide, the release of histamine was accompanied by degranulation of isolated rat mast cells, in a dose-dependent manner. However, the dynorphin-induced histamine release was not inhibited by antagonists such as naloxone or leucine-enkephalin. These observations indicate that the release of histamine by dynorphin is not mediated by opioid receptors distributed on the mast cells. Thus, histamine release from the mast cells induced by various chemical agents, including tubocurarine, might not be mediated by receptors specific for these chemicals.

The present results provide direct evidence that the increase in histamine concentration in the plasma of tubocurarine-treated animals is the result of the action of tubocurarine on the mast cells causing them to release histamine. However, this effect is not mediated via the acetylcholine receptors.

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CARBON DIOXIDE CLEARANCE DURING HIGH FREQUENCY JET VENTILATION

Effect of Deadspace in a Lung Model

A. J. MORTIMER, J.-L. BOURGAIN, J. UPPINGTON AND M. K. SYKES

SUMMARY

The effects of the volume and length of deadspace on the clearance of carbon dioxide from a lung model have been investigated during high frequency jet ventilation (HFJV) at 1, 3 and 5 Hz. At 1 Hz, increasing the volume of the deadspace without changing the length caused a reduction in the clearance of carbon dioxide. At 5 Hz, an increase in the length of deadspace decreased carbon dioxide clearance, whilst an increase in volume had no effect. Since the delivered tidal volume was less than the volume of the morphological deadspace at this frequency, the elimination of carbon dioxide must have been accomplished by mechanisms which are not considered important at normal tidal volumes and frequencies. Furthermore, the clearance of carbon dioxide at 5 Hz was very inefficient compared with that at 1 Hz. It is concluded that, during HFJV, carbon dioxide is cleared most efficiently when the frequency is low enough for the delivered tidal volume to be greater than the volume of the morphological deadspace.

During high frequency jet ventilation (HFJV) the clearance of carbon dioxide appears to be very variable. This may be the result of differences in the volume of gas delivered to the trachea or of variations in the pattern of gas transport in the conducting airways and alveoli. Since it is difficult to collect true mixed expired gas during HFJV, we have studied the effects of adding deadspaces of different lengths and volumes on the elimination of carbon dioxide from a lung model.

METHODS

The model lung (Manley Lung Ventilator Performance Analyser) consisted of a spring-loaded bellows with a variable orifice to simulate airway resistance. The compliance was adjusted to 50 ml cm H_2O^{-1} and the airway resistance to 5 cm H_2O litre^{-1} s^{-1}. The end-expiratory lung volume was 500 ml. The lung was ventilated with a high frequency jet ventilator set to deliver different tidal volumes at frequencies of 1, 3 and 5 Hz. The clearance of carbon dioxide from the lung was measured by recording the flow rate of carbon dioxide which had to be added to the lung to maintain a mean concentration of 6% at each ventilator setting. Tidal and minute volumes were determined from the variations in pressure within a box plethysmograph which surrounded the lung (fig. 1).

High frequency jet ventilator and circuit

The jet ventilator was constructed in accordance with the guidelines given by Carlon and colleagues (1981) except that, instead of a single electronically timed solenoid valve, four valves (1.3 mm orifice, Sirai, Milan, Italy) were mounted in parallel. Medical air at a pressure of 400 kPa was supplied to the valves through a variable pressure regulator. The duration of each pulse was controlled by the

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A. J. MORTIMER, B.SC., M.B., B.S., D.(OBST.). R.C.O.G., F.F.A.R.C.S.; J.-L. BOURGAIN,* M.D.; J. UPPINGTON, M.B., B.S., D.(OBST.). R.C.O.G., D.A., F.F.A.R.C.S., M. K. SYKES, M.A., M.B., B.CHIR., F.F.A.R.C S., F.F.A.R.A.C.S. (HON); Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.

*Present address: Institute Gustave Roussy, Service d'Anesthésie, Rue Camille Desmoulins, 94805 Villejuif Cedex, Paris, France.

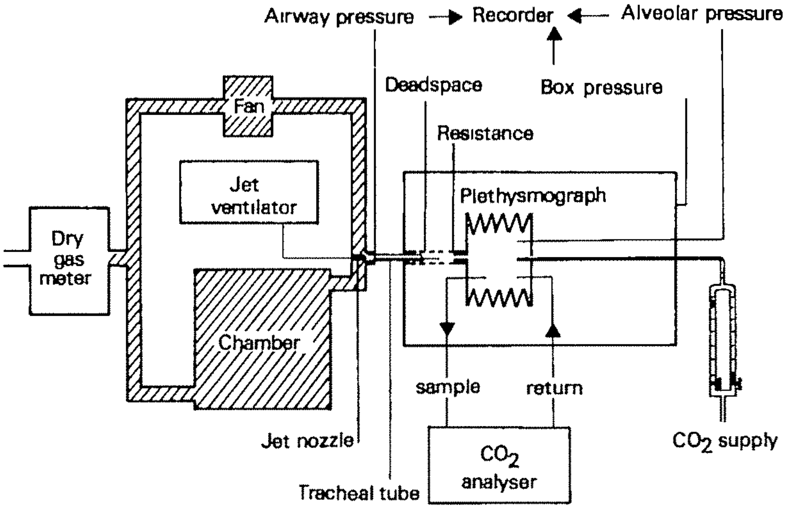

FIG. 1. Experimental arrangement: carbon dioxide is supplied to the interior of the model lung which is placed inside the plethysmograph. HFJV is delivered to the lung through deadspaces of known length and volume from a nozzle fixed in the T-piece. Minute ventilation of the lung is determined from the pressure changes in the plethysmograph whilst the volume delivered from the jet nozzle is collected in the ventilation circuit (hatched area) and measured by the dry gas meter.

cycling frequency and the duty cycle (the proportion of each cycle during which the valve is open). The flow rate was controlled by the number of valves opening simultaneously and by the pressure gradient across the valves.

The pulses of air were delivered to the lung through 1.5 m of non-compliant tubing (4 mm i.d.) to a 1.8-mm brass nozzle incorporated in a T-piece. The T-piece was connected directly to the proximal end of a 9-mm i.d. cuffed Portex tracheal tube so that the jet was directed down the axis of the tube. The cuffed end of the tracheal tube formed an airtight seal with the proximal end of the deadspace under investigation, the distal end of the latter being connected directly to the model lung. The side ports of the T-piece had 22-mm tapers to which 1-m lengths of corrugated rubber tubing were attached. The opposite ends of these tubes were joined by a second T-piece through which gases were led to a calibrated dry gas meter (Parkinson Cowan, CD1). This meter measured the volume of gas entering the circuit through the jet plus the volume of carbon dioxide added to the lung. Thus the minute volume of the jet could be calculated. The circuit contained a large chamber to minimize fluctuations in pressure when the jet entrained gas. A recirculating fan promoted mixing of the air in the circuit with the carbon dioxide-rich expired gas. The volume of the complete circuit, which included the chamber, both lengths of 22-mm tubing and the T-pieces, was 65.5 litre measured by carbon dioxide dilution. The resistance of the circuit to gas flow was less than 2 cm H_2O litre^{-1} s^{-1}. Any errors attributable to rebreathing have been ignored since, in a previous investigation using the same circuit and lung model with a non-linear airway resistance, we have found entrainment to be small (up to 20%), and to occur only at 1 Hz and with low I:E ratios (Mortimer and Bourgain, 1983).

The artificial deadspaces were constructed from rigid plastic tubing. Two were short in length (17 cm), one of these being small in volume (16 ml) and the other large in volume (40 ml). The third deadspace was both long (35 cm) and large (40 ml). All three deadspaces had the same resistance to continuous flow (1 cm H_2O at 50 litre min^{-1}). The total calculated volumes of morphological deadspace (which included the tracheal tube, the artificial deadspace and the tubing leading into the model lung) were 73 ml (short, small volume deadspace), 97 ml (short, large volume deadspace) and 102 ml (long, large volume deadspace).

Mean alveolar pressures were recorded from the inside of the bellows and mean airway pressures from the distal end of the deadspace tubing using air-filled catheters (1.5 mm i.d.) and transducers. Alveolar pressure was sensed with an optical defocusing pressure transducer (Mercury Electronics, UK) incorporating a 0–30 cm H_2O pressure cell. Airway pressure was sensed with a Druck PDCR 75 transducer. The signals from both transducers were displayed on a heated stylus recorder (Devices M19), and mean values were obtained by electronic damping.

Measurement of tidal and minute volumes

The box plethysmograph had an internal volume of 125 litre. Changes in pressure were detected with an air filled pressure transducer (EMT 33, Elema Schönander, Sweden) connected to the box by a short (2-cm) piece of rigid plastic tubing (3 mm i.d.). The pressure signals were displayed on an ink-jet recorder (EMT 34, Elema Schönander, Sweden). The frequency response of the transducer alone was within ±5% up to 50 Hz. The frequency response of the box plethysmograph and pressure recording system was tested by oscillating the air inside the box with a rolling diaphragm piston pump and was found to be flat up to 15 Hz. At higher frequencies, vibration from the piston pump interfered with the recordings.

During each investigation the plethysmograph was calibrated (with a 1-litre syringe) by the rapid injection of 500 ml of air either as a single bolus or in 100-ml increments. The increase in pressure in the plethysmograph decayed over 50–75 s, the initial pressures (adiabatic compression) being greater than the final pressures (isothermal compression) by 26% ± 2 SD at volumes up to 500 ml. All volumes were measured at ambient temperature and pressure dry (ATPD).

The validity of the calibration procedure was confirmed by comparing the box pressures recorded when increments of air were added to the test lung inside the box, and when the same volumes of air were added directly to the box but with the lung sealed off inside. The results for each procedure were identical.

Measurement of carbon dioxide clearance

Carbon dioxide was supplied to the interior of the bellows from one of three parallel mounted rotameters. The first regulated flow up to 100 ml min^{-1}, the second, flow up to 1 litre min^{-1} and the third, flow up 5 litre min^{-1}.

The concentration of carbon dioxide inside the bellows was measured by passing a 150–200-ml min^{-1} sample through an infra-red analyser (Gould MK III) calibrated from 0 to 10% carbon dioxide in air and returning this to the bellows. At each ventilator setting the flow rate of carbon dioxide into the lung was increased progressively until a mean concentration of 6% was recorded. The flow rates were recorded at ATPD. Equilibrium was reached quickly at 1 Hz but, at 5 Hz, 15–20 min was required to achieve a steady state.

Experimental design

Two complementary studies were performed.

First: the three deadspaces were randomly interchanged and the elimination of carbon dioxide determined at 1, 3 and 5 Hz. The pressure gradient across the solenoid valves was held constant at 300 kPa. At each frequency nine different tidal volumes were obtained by the use of one, two or four solenoid valves at inspiratory: expiratory (time) ratios of 1:1, 1:2 and 1:4.

Second: the T-piece, tracheal tube and artificial deadspace were replaced with a Perspex tube 35 cm long and 9 mm i.d. The proximal end of this tube was connected to a modified T-piece which permitted the jet to be advanced down the axis of the tube to the distal end, the axial position of the jet being maintained with guidewires. The difference in volume of the morphological deadspace between the proximal and distal positions of the jet nozzle was 20 ml. The clearance of carbon dioxide was determined at 1, 3 and 5 Hz at each nozzle position using the same nine ventilator settings as were used in the first study.

Statistical analysis

The data obtained from both investigations were analysed by least squares linear regression analysis. From the first experiment, the regression lines relating the clearance of carbon dioxide and tidal volume for each deadspace at 1, 3 and 5 Hz were tested for homogeneity of variance with Bartlett's test (Snedecor and Cochrane, 1980). The slopes were then compared by analysis of variance. When the slopes were not significantly different, the elevation of the lines was compared by the same method. Since three sets of data were compared at each frequency, statistical significance was accepted when $P < 0.01$.

RESULTS

First study

The tidal volumes recorded by the box plethysmograph were similiar for each deadspace

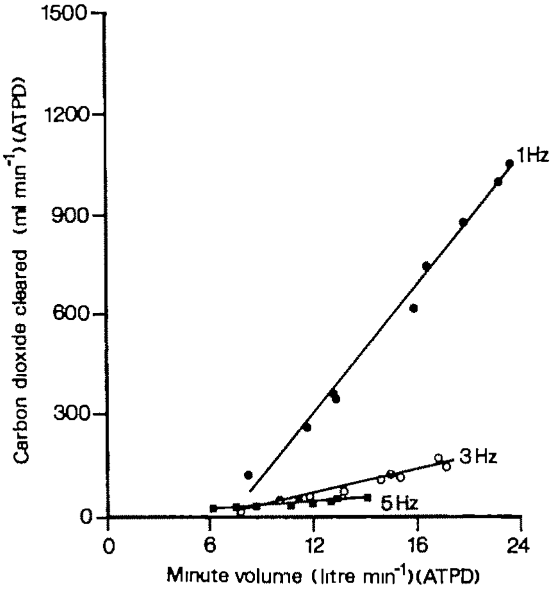

FIG. 2. Relationship between carbon dioxide cleared and minute ventilation of the lung model at 1 Hz (●), 3 Hz (○) and 5 Hz (■) with the long, large deadspace in position.

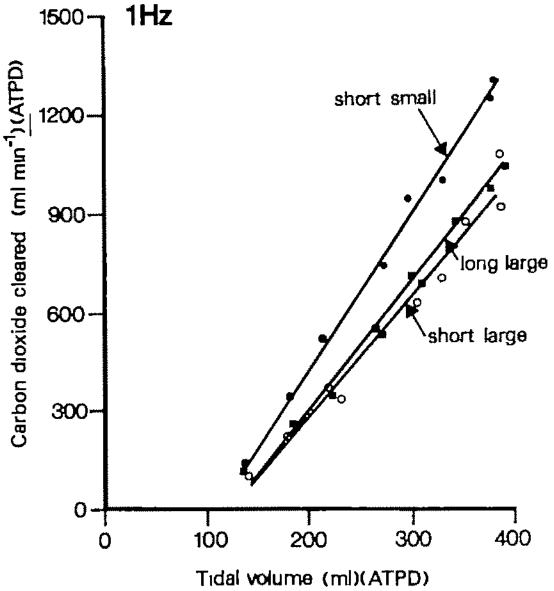

FIG. 3. Relationship between carbon dioxide cleared and tidal volume at 1 Hz for the short, small volume (●), short, large volume (○) and long, large volume (■) deadspaces. For each reading, V_T exceeds V_D. The regression lines show that carbon dioxide clearance is decreased when the volume of the deadspace is increased, independent of a change in the length.

and decreased as the frequency of ventilation increased.

There was a strong positive linear relationship at each frequency between the clearance of carbon dioxide and minute ventilation ($P < 0.001$), the increase in carbon dioxide clearance for a given increase in minute volume being greatest at 1 Hz, least at 5 Hz and intermediate at 3 Hz (fig. 2). However, the relationship between the carbon dioxide cleared and tidal volume at each frequency varied with the dimensions of the deadspace (figs 3, 4 and 5).

At 1 Hz (fig. 3) the slopes of the regression lines of carbon dioxide cleared on tidal volume were not significantly different. However, the magnitude of carbon dioxide cleared, judged from the elevation of the regression lines, was significantly greater ($P < 0.001$) with the short, small volume deadspace compared with the two large volume deadspaces. There was no significant difference between the latter (table I). At this frequency, the tidal volume (V_T) exceeded the total morphological deadspace volume (V_D) by a factor which ranged from 1.3 to 5.2 and the length of each deadspace had no effect on carbon dioxide elimination.

At 3 Hz (fig. 4), V_T was always smaller than at 1 Hz and ranged from 0.4 to 1.6 times V_D (table I). With the short, small volume deadspace in position, V_T exceeded V_D in five measurements. When these readings were included in the calculation of the regression line (fig. 4), the slope of carbon dioxide clearance was significantly greater from this deadspace ($P < 0.001$) compared with the two large volume deadspaces (table I), there being no significant difference between the latter. However, when these figures were eliminated so that all comparisons were made with V_T less than V_D, there were no significant differences between the slopes of all three regression lines.

The tidal volumes at 5 Hz (fig. 5) were smaller than at 3 Hz and ranged from 0.2 to 0.6 times V_D (table I). The slopes of the regression lines of carbon dioxide cleared were identical for the two deadspaces which were short in length. At the higher tidal volumes, the clearance of carbon dioxide from these was greater than from the long deadspace (table I). At 5 Hz, therefore, the length of the deadspace was more important than the volume in influencing carbon dioxide elimination.

Second study

There were no significant differences between the mean airway and mean alveolar pressures

TABLE I. *V*T:*V*D *ratios and regression equations for carbon dioxide clearance* (y) *on tidal volume* (x) *for each deadspace at 1, 3 and 5 Hz. Statistical comparison of the slopes is included together with comparison of the elevation of each line when the slopes are not significantly different*

Frequency (Hz)		Deadspace length	Type of volume	Tidal volume: deadspace ratio (*V*T:*V*D) (range)	*n*	*y*		*r*	*P*
						Slope	Intercept		
1	a	Short	Small	1.9–5.2	8	4.73*x*	−529.35	0.99	< 0.001
	b	Short	Large	1.4–3.9	9	3.62*x*	−431.05	0.98	< 0.001
	c	Long	Large	1.3–3.8	9	3.93*x*	−482.17	0.99	< 0.001
					a *v*. b	ns	$P < 0.001$		
					a *v*. c	ns	$P < 0.001$		
					b *v*. c	ns	ns		
3	a	Short	Small	0.6–1.6	9	5.07*x*	−220.28	0.97	< 0.001
	b	Short	Large	0.4–1.1	9	1.90*x*	−34.35	0.92	< 0.001
	c	Long	Large	0.4–1.1	9	2.27*x*	−88.15	0.98	< 0.001
					a *v*. b	$P < 0.001$	—		
					a *v*. c	$P < 0.001$	—		
					b *v*. c	ns	$P < 0.001$		
5	a	Short	Small	0.3–0.6	9	3.98*x*	−61.03	0.99	< 0.001
	b	Short	Large	0.2–0.5	9	3.99*x*	−65.26	0.98	< 0.001
	c	Long	Large	0.2–0.5	9	1.35*x*	−14.26	0.94	< 0.001
					a *v*. b	ns	ns		
					a *v*. c	$P < 0.001$	—		
					b *v*. c	$P < 0.001$	—		

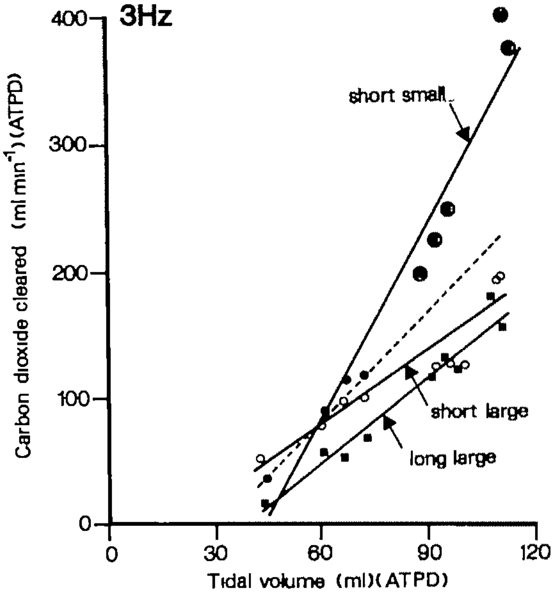

FIG. 4. Relationship between carbon dioxide cleared and tidal volume at 3 Hz for the short, small volume (●), short, large volume (○) and long, large volume (■) deadspaces. The encircled symbols (◉) indicate the measurements of carbon dioxide clearance from the short, small deadspace when *V*T is greater than 1.2 times *V*D. The regression line when these points are omitted from the analysis, is represented by the dotted line. The regression lines suggest that when *V*T exceeds *V*D, carbon dioxide elimination is much more efficient compared with when *V*T is smaller than *V*D.

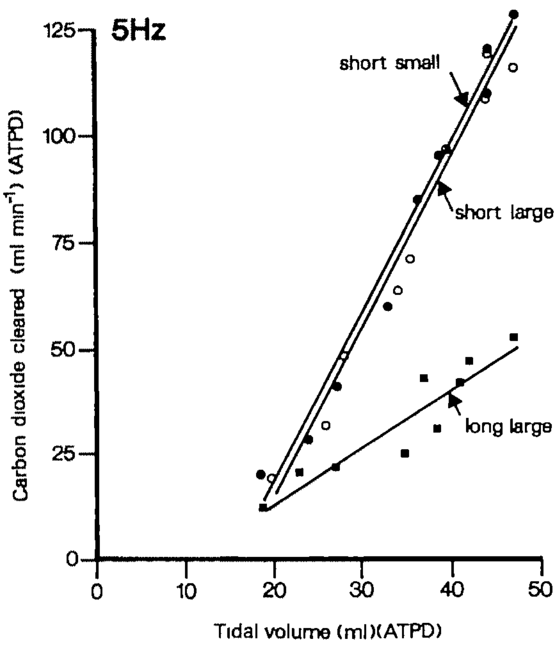

FIG. 5. Relationship between carbon dioxide cleared and tidal volume at 5 Hz for the short, small volume (●), short, large volume (○) and long, large volume (■) deadspaces. For each measurement, *V*T is smaller than *V*D. The regression lines suggest that carbon dioxide clearance is affected more by a change in the length of the deadspace than by a change in the volume.

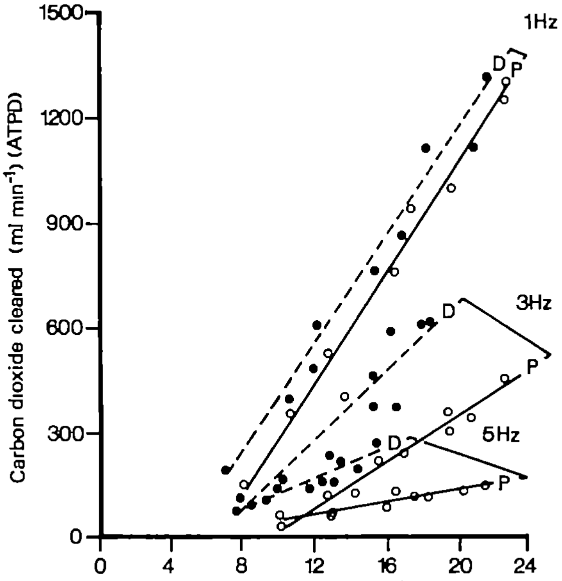

FIG. 6. Relationship between carbon dioxide cleared and minute ventilation at 1, 3 and 5 Hz, comparing proximal (P) with distal (D) injection. At each frequency, the same minute volume clears more carbon dioxide from the lung when jet injection is distal compared with proximal.

whether the jet was situated proximally or distally. The clearance of carbon dioxide at any minute volume was greatest at 1 Hz and least at 5 Hz (fig. 6). However, for a given minute volume at each frequency, distal placement of the nozzle resulted in the greatest carbon dioxide clearance. The increase in minute volume required to produce a normal carbon dioxide clearance (200 ml min^{-1}) with the jet in a proximal position was approximately 1.5 litre min^{-1} at 1 Hz, 5 litre min^{-1} at 3 Hz and 11 litre min^{-1} at 5 Hz.

DISCUSSION

Several features of relevance to the elimination of carbon dioxide during HFJV are illustrated by these results. In both studies a good correlation was observed at each frequency between the clearance of carbon dioxide and the minute and tidal ventilation. Since the different volumes at each frequency were obtained by changing both the number of solenoid valves opening and the duration of air flow, it appears that the clearance of carbon dioxide is related primarily to V_T and not to the inspiratory : expiratory time ratio. These results agree with those reported by Rossing and co-workers (1981) during high frequency oscillation (HFO) in patients. They found that, at frequencies between 30 and 200–300 cycles min^{-1}, carbon dioxide clearance was linearly related to both V_T and the product of V_T and frequency. At frequencies greater than 3 Hz, the elimination of carbon dioxide was influenced more by the delivered volume than by the frequency. In a separate study in dogs (Bourgain, Mortimer and Sykes, 1986) in which carbon dioxide clearance during HFJV was determined by a completely different method, we have observed similiar linear relationships between the elimination of carbon dioxide and both minute and tidal ventilation at frequencies up to 5 Hz.

The elimination of carbon dioxide was most efficient when the frequency was 1 Hz and V_T exceeded V_D (fig. 2). At the higher frequencies, when V_T was smaller than V_D, carbon dioxide elimination was less than the normal production of 200 ml min^{-1} despite the use of large minute volumes. Similar observations have been recorded in dogs (Chakrabarti and Sykes, 1980; Colgan, Teneyck and Sawa, 1983; Weinmann, Mitzner and Permutt, 1984) and in rabbits (Fletcher and Epstein, 1982).

The use of a single airway–alveolus lung model with non-linear resistance and compliance characteristics (Chakrabarti and Sykes, 1976) may be criticized on the grounds that it is a gross simplification of the normal anatomy. However, the compliance was linear over the range of volumes studied (20–400 ml) and the use of such a model permits greater control of variables and increases the range of measurements which can be made.

The results in the first series of experiments suggest that, at 1 Hz, the elimination of carbon dioxide was decreased by an increase in the volume of the deadspace, but that its length had no effect whereas, at 5 Hz, carbon dioxide elimination was decreased by an increase in length but was not affected by an increase in volume. At 3 Hz, when V_T was less than V_D, length also appeared to be more important than volume. These observations suggest that, at 1 Hz, V_T was sufficiently large to flush out V_D and that ventilation was primarily the result of convective transport. If this was the case, then the mean alveolar concentration of carbon dioxide ($F_{A_{CO_2}}$) calculated from the measured carbon dioxide clearance ($\dot{V}_{CO_2}$) and alveolar ventilation ($\dot{V}_A$—

derived from the minute volume and the morphological deadspace volume), should be the same as the $F\mathrm{A_{CO_2}}$ used in the experiment (0.06). To verify the results at 1 Hz, $F\mathrm{A_{CO_2}}$ was calculated at each ventilator setting for the two extremes of deadspace (short length, small volume and long length, large volume) from the relationship:

$$F\mathrm{A_{CO_2}} = \frac{\dot{V}\mathrm{CO_2\,ml\,min^{-1}}}{\dot{V}\mathrm{A\,ml\,min^{-1}}} \qquad (1)$$

The calculated value of 0.058 ± 0.008 SD ($n = 17$) was very close to the set value which was (0.06), thus confirming that gas exchange could be explained by conventional physiological principles.

At 3 Hz, the clearance of carbon dioxide was greatest from the deadspace which was short in length and small in volume (fig. 4). The tidal volume exceeded $V\mathrm{D}$ in 10 measurements out of the total of 27, but in only five of these was the calculated $F\mathrm{A_{CO_2}}$ (0.059 ± 0.007 SD) close to the set level of 0.06. The latter values were associated with the short length, small volume deadspace (fig. 4), when $V\mathrm{T}$ exceeded $V\mathrm{D}$ by a factor which ranged from 1.2 to 1.6. This suggests that, under these circumstances, gas transport was primarily as observed at 1 Hz. However, the calculated $F\mathrm{A_{CO_2}}$ for the other five measurements (0.12 ± 0.053 SD) when $V\mathrm{T}$ was between 1.0 and 1.2 times $V\mathrm{D}$, was twice that used in the study. This indicates that the effective alveolar ventilation was greater than that calculated from equation (1), and implies that the effective deadspace volume was smaller than the volume of the total morphological deadspace.

At 5 Hz, $V\mathrm{T}$ was always smaller than $V\mathrm{D}$. The length of $V\mathrm{D}$, as opposed to the volume, became dominant in influencing the clearance of carbon dioxide. Elimination of carbon dioxide always exceeded the basal loss from the lung (5–10 ml min^{-1}) which occurred when the bellows concentration was 6% in the absence of ventilation, but was markedly lower than normal carbon dioxide production.

In the second series of experiments distal placement of the jet decreased both the length and volume of the deadspace. The difference in volume (20 ml) was similar to the difference in volume between the other deadspaces, but the difference in length (35 cm) was twice as great. At both 3 Hz and 5 Hz, distal injection more than doubled carbon dioxide clearance. At 1 Hz the difference in clearance was much smaller, the increase in $V\mathrm{T}$ required to achieve the same clearance being closely related to the added volume of the deadspace (fig. 6).

The mechanisms which may account for adequate elimination of carbon dioxide during small volume, high frequency ventilation have been reviewed recently (Chang, 1984; Drazen, Kamm and Slutsky, 1984). The consensus of opinion is that, whilst delivery of carbon dioxide from pulmonary blood to the alveoli occurs by molecular diffusion, four mechanisms acting in concert can account for the transport of carbon dioxide from the alveoli to the mouth. First, direct ventilation of the most proximal and centrally situated alveoli, since their deadspace is small relative to the peripheral alveoli; second, mixing within the airways as a result of transfer of gas between alveoli with different time constants (Pendelluft); third, convective streaming which results from differences between the inspiratory and expiratory velocity profiles; and fourth, augmented dispersion in which gas mixing occurs longitudinally by radial diffusion from an axial velocity profile which is non-uniform (Taylorian dispersion).

In our first experiment at 1 Hz and 3 Hz, the clearance of carbon dioxide was greatest when $V\mathrm{T}$ exceeded 1.2 times $V\mathrm{D}$ and behaved in accordance with the conventional concept of alveolar ventilation (equation (1)). At 3 Hz and 5 Hz, however, when $V\mathrm{T}$ was less than 1.2 times $V\mathrm{D}$, appreciable quantities of carbon dioxide were still removed from the lung. The higher level of effective alveolar ventilation ($\dot{V}\mathrm{A}^\star$) therefore, must have been achieved by a reduction in the effective deadspace volume ($V\mathrm{D}^\star$). This was calculated by rearranging equation (1) as follows:

$$\dot{V}\mathrm{A}^\star = \frac{\dot{V}\mathrm{CO_2\,ml\,min^{-1}}}{F\mathrm{A_{CO_2}\,ml\,min^{-1}}} \qquad (2)$$

where the value for $F\mathrm{A_{CO_2}}$ was 0.06 as used in the study. The resultant value of $\dot{V}\mathrm{A}^\star$ was then used to derive $V\mathrm{D}^\star$ from the measured minute ventilation.

In figure 7 the calculated $\dot{V}\mathrm{A}^\star$ is compared with the $\dot{V}\mathrm{A}$ derived from $\dot{V}\mathrm{A} = f\,(V\mathrm{T} - V\mathrm{D}^{\mathrm{morph}})$ at 1, 3 and 5 Hz. The regression line for $\dot{V}\mathrm{A}$ greater than 5 litre min^{-1} shows there is a good correlation between $\dot{V}\mathrm{A}$ and $\dot{V}\mathrm{A}^\star$. At lower values of $\dot{V}\mathrm{A}$ this correlation no longer holds, $\dot{V}\mathrm{A}^\star$ remaining positive down to $\dot{V}\mathrm{A}$ values of minus 25 litre min^{-1}. This suggests that, within this range, $V\mathrm{D}^\star$ becomes smaller than $V\mathrm{D}$. Figure 8 illustrates the

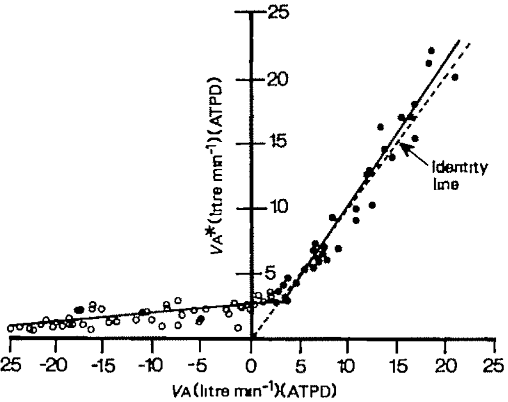

FIG. 7. Relationship between the effective alveolar ventilation ($\dot{V}_A^*$—derived from equation (2)) and the alveolar ventilation ($\dot{V}_A$—derived from equation (1)). All measurments at each frequency are included. The solid circles (●) represent the results when V_T is greater than 1.2 times V_D whilst the open circles (○) represent the results when V_T is smaller than 1.2 times V_D.

relationship between $\dot{V}_A^*$ and V_T at 3 Hz with the short length, small volume deadspace. The data are presented as two separate regression lines, one which includes the results where V_T is greater than V_D and the other where V_T is smaller than V_D. This shows that a reduction in V_T produces a smaller reduction in $\dot{V}_A^*$ when V_T is less than V_D, than when it is greater than V_D. It also demonstrates that there is a transitional zone where ventilation by bulk flow gives way to other mechanisms discussed previously. The x-axis intercept of the regression line where V_T exceeds V_D gives a reasonable approximation to the true morphological deadspace volume (73 ml), thus confirming that bulk flow is dominant under these circumstances.

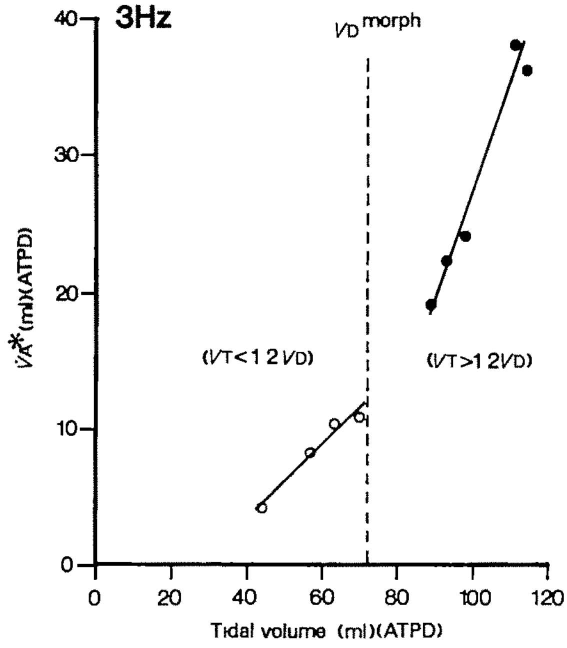

FIG. 8. Relationships between effective alveolar ventilation ($\dot{V}_A^*$) and delivered tidal volume (V_T) at 3 Hz, when V_T exceeds 1.2 times V_D (●) and when V_T is less than 1.2 times V_D (○). The true morphological deadspace volume is shown by the vertical line.

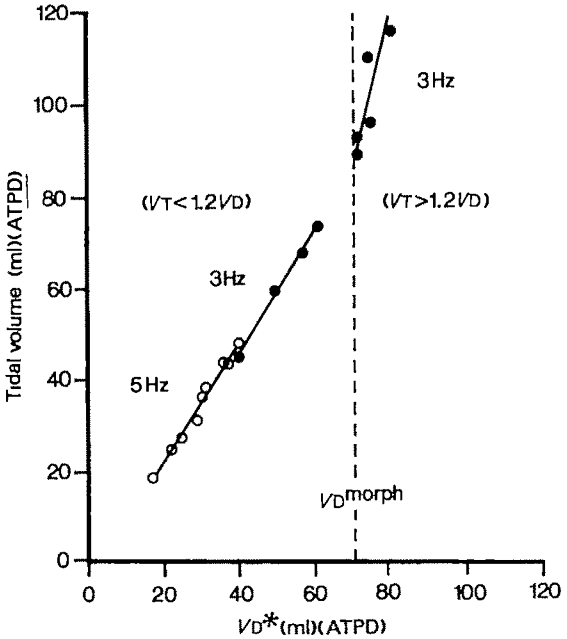

FIG. 9. Relationships between delivered tidal volume (V_T) and effective deadspace volume (V_D^*) at 3 Hz (●) and 5 Hz (○) for the short, small volume deadspace. The results at 3 Hz are shown as two regression lines, one representing V_T greater than 1.2 times V_D and the other where V_T is smaller than 1.2 times V_D. At 5 Hz, all measurements of V_T are less than V_D.

The relationships between V_T and V_D^* at 3 and 5 Hz are shown for the short length, small volume deadspace in figure 9. The progressive linear reduction in V_D^* with decrease in V_T which occurs when V_T is less than V_D, appears to be independent of frequency since the slopes of the regression lines are the same. The results for the other deadspaces when V_T was smaller than V_D were similar.

These observations suggest that the magnitude of alveolar ventilation at any frequency is governed by the relationship betwwen V_T and V_D. The reduction in V_D with decreasing V_T was first described 71 years ago by Henderson, Chillingworth and Whitney (1915). From studies on axial gas flow through a tube, and measurement of the carbon dioxide content of successive fractions of expired air from man, they concluded that considerable elimination of carbon dioxide occurred even when V_T was smaller than V_D. This provided an explanation for the ability of a dog to maintain adequate gas exchange when V_T was smaller than V_D, as occurs during panting. These findings were confirmed by Briscoe, Forster and Comroe (1954), who found that, when subjects inspired volumes which were smaller than the Fowler deadspace volume, V_D decreased. They postulated that the inspired air passed through the airways as an elongated cone, leaving static layers of air close to the walls of the trachea and bronchi, thereby reducing the effective volume of the airways.

Other, more recent, observations support our findings. Isabey, Harf and Chang (1984), have introduced the concept of core deadspace to describe the reduction in effective deadspace which they observed in a lung model ventilated between 5 and 40 Hz. They found that, when V_T exceeded 1.2 times V_D, the clearance of carbon dioxide could be attributed to bulk transport of gas. However, when V_T ranged from 0.8 to 1.2 times V_D, the effective tidal volume was greater than the measured V_T. They concluded that the volume of the effective deadspace was smaller than the volume of the morphological deadspace, and that direct alveolar ventilation through the core of the deadspace made a significant contribution to the elimination of carbon dioxide. In another study, in dogs at constant arterial P_{CO_2} ventilated at frequencies between 0.2 and 8 Hz, Weinmann, Mitzner and Permutt (1984) found a marked and progressive decrease in physiological V_D which had been measured during low frequency, large volume ventilation.

The implications of our studies on the clearance of carbon dioxide from a lung model can be summarized as follows. First, when V_T exceeds V_D by a factor of 1.2 or more, the elimination of carbon dioxide occurs predominantly by bulk flow. This mechanism appears to be independent of frequency between 1 and 3 Hz. The elimination of carbon dioxide is impaired by an increase in the volume of V_D, but is unaffected by a change in the length. Second, when V_T is less than 1.2 times V_D, bulk transport of carbon dioxide is reduced and other mechanisms assume importance. Under these circumstances the efficiency of carbon dioxide removal is greatly affected by the length of the path between the jet and the lung. Elimination of carbon dioxide is much less efficient and may be inadequate to remove a normal level of carbon dioxide production.

Several reports have confirmed the importance of delivering the fresh gas close to the carina. Davey, Lay and Leigh (1982) found that the efficiency of ventilation was enhanced in a patient when the fresh gas was delivered through a distal jet compared with a proximal jet. Smith, Sjöstrand and Babinski (1983) ventilated dogs at normocapnia with tidal volumes which were approximately 20% smaller when the jet was delivered near the distal end of the tracheal tube compared with the proximal end. During HFO at frequencies up to 12 Hz, Rossing and co-workers (1984) observed an improvement of up to 50% in the elimination of carbon dioxide from patients, when the fresh gas bias flow was changed from the proximal to the distal end of the tracheal tube.

The evidence, together with our own observations, confirm that, during high frequency jet ventilation, the elimination of carbon dioxide is most efficient when V_T exceeds V_D by a factor of 1.2 or more. This can be achieved in two ways: first, by an absolute reduction in V_D through delivering the fresh gas as distal as possible in the trachea and, second, by ventilating at a frequency which is sufficiently low to ensure that V_D is exceeded by the delivered V_T.

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EFFERENT PHRENIC NERVE ACTIVITY DURING INDUCED CHANGES IN ARTERIAL PRESSURE

E. M. GRUNDY, M. K. CHAKRABARTI AND J. G. WHITWAM

SUMMARY

Efferent activity in the phrenic nerve was recorded during induced hypotension and hypertension in anaesthetized, paralysed, artificially ventilated dogs. Changes in arterial pressure were induced with infusions of sodium nitroprusside, noradrenaline and angiotensin II, after which ventilation was adjusted to return the Pa_{CO_2} *near to control values. The* Pa_{O_2} *was maintained above chemoreceptor threshold throughout. When a steady state was achieved quantitative measurements of phrenic nerve activity were made. In six dogs an increase in mean arterial pressure from 114 to 167 mm Hg caused a mean reduction of phrenic nerve activity of 28%. In six dogs a decrease in mean arterial pressure from 128 to 82 mm Hg caused an increase in phrenic nerve activity of 22%. This shows that the reduction in arterial pressure induced by vasodilator drugs causes a major sustained stimulus to respiration, while increase in arterial pressure causes marked respiratory depression.*

Stimulation of the systemic baroreceptors inhibits respiration (Heymans and Neil, 1958). In most of the studies in which this has been demonstrated, pressure has been applied to an isolated vascular area containing baroreceptors, or the carotid sinus and aortic nerves have been stimulated electrically. Hitherto there has not been a great deal of work on the effects of induced alterations in arterial pressure, in otherwise intact animals, on central respiratory activity. Garcia and Cherniack (1967) observed that increasing systemic arterial pressure with noradrenaline inhibited phrenic nerve activity in apnoeic dogs. Grunstein, Derenne and Milic-Emili (1975) showed that the transient inflation of an intra-aortic balloon caused an acute increase in systemic arterial pressure, a decrease in tidal volume and an increase in the inspiratory time in cats. However, both these studies were concerned with the effects of acutely induced hypertension and, hence, baroreceptor stimulation. Although Miserocchi and Quinn (1980) observed the effects of haemorrhage on respiration in spontaneously breathing cats, the absence of studies on the effects of hypotension induced with vasodilator drugs, and also during artificial ventilation, is surprising in view of the potential interest in this subject.

The present study was undertaken to quantify the changes in phrenic nerve activity (in intact animals under steady state conditions) in response to both increases and decreases in arterial pressure.

MATERIALS AND METHODS

Investigations were performed on 10 unpremedicated mongrel dogs weighing between 13 and 20 kg. Anaesthesia was induced with methohexitone 15 mg kg^{-1} i.v. after which a cuffed tracheal tube was passed. The animal's lungs were ventilated with a Starling pump (intermittent positive pressure ventilation, IPPV) at a rate of 10 b.p.m. and a femoral artery and vein were cannulated.

Anaesthesia was maintained with a 1% solution of α-chloralose, initially in a bolus dose of 30 mg kg^{-1} followed by a continuous i.v. infusion of 15–20 mg kg^{-1} h^{-1}. Suxamethonium 1–2 mg kg^{-1} h^{-1} was administered to provide

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E. M. GRUNDY,* B.SC., M.R.C.P., F.F.A.R.C.S; M. K. CHAKRABARTI, B.SC., M.PHIL.; J. G. WHITWAM, M.B., CH.B., PH.D., F.R.C.P., F.F.A.R.C.S.; Department of Anaesthetics, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS.

*Present address: Department of Anaesthetics, The Middlesex Hospital, Mortimer Street; London W1.

Correspondence to J. G. W.

neuromuscular blockade. Airway and arterial pressures were recorded using resistance strain gauges (S.E. Laboratories) calibrated against water and mercury columns, respectively. The end-tidal carbon dioxide concentration was measured with an infra-red carbon dioxide analyser (Hartmann Braun, URAS 4) calibrated with preanalysed gas mixtures.

The phrenic nerve was exposed in the neck, dissected, desheathed and cut distally. It was placed on silver–silver chloride electrodes in a pool of mineral oil to record efferent activity. The signal from the recording electrode was passed through a preamplifier (Tektronix RM122) and a differential amplifier (Tektronix 2063) before being displayed. In addition, the electroneurogram was rectified and integrated (Neurolog 90-Digitimer). All signals were displayed on an ultra-violet recorder (S.E. Laboratories type 2112).

In order to ensure the synchronization of bursts of phrenic nerve activity with the respiratory cycle, relatively large tidal volumes (approximately 20 ml kg^{-1}) were used. Oxygen was added to the inspired gas to maintain a Pa_{O_2} greater than 23 kPa. Intermittent arterial blood analysis for Pa_{O_2}, Pa_{CO_2} and pH was performed using a Radiometer ABL1 blood-gas analyser. Sodium bicarbonate was administered to maintain the base excess and pH within a narrow range. Oesophageal temperature was maintained in the range 37–38 °C.

In view of the large tidal volumes carbon dioxide was administered to maintain an FE_{CO_2} of approximately 6% and the Pa_{CO_2} was maintained around 5.8 kPa. Along with the large tidal volume, this ensured that the bursts of phrenic nerve activity (PNA) remained synchronized with the ventilator throughout each study. In addition, this technique allowed the Pa_{CO_2} to be changed in either direction by altering the FI_{CO_2} without having to change the VT or respiratory rate.

After the completion of the surgical preparation, a period of 30 min was allowed for stabilization. Control measurements were obtained of blood-gas tensions, phrenic nerve activity, arterial pressure and heart rate.

An initial pilot study showed that a bolus dose of sodium nitroprusside (SNP) 10 mg decreased mean arterial pressure (MAP) and increased the PNA while a bolus of noradrenaline (NA) 0.5 mg produced the opposite result. However, when MAP increased, the FE_{CO_2} and Pa_{CO_2} decreased, whereas a decrease in MAP caused increases in FE_{CO_2} and Pa_{CO_2}. Thus, the changes in PNA (figs 1 and 2) could have been the result of the changes in Pa_{CO_2}, which were the result of alterations in ventilation:perfusion ratios in the lungs, and not results of the changes in MAP *per se*. Angiotensin II (AII) caused effects similar to those of NA.

In subsequent studies "steady states" were achieved so that, by maintaining MAP constant, the Pa_{CO_2} could be adjusted and maintained close to control values throughout each period of observation. The arterial pressure was either decreased with SNP in a dose sufficient to produce a decrease of approximately 45 mm Hg, or was increased with angiotensin II. The vasoactive drug was given as an initial bolus followed by an infusion to maintain a constant MAP. The carbon dioxide added to the inspired gas mixture was adjusted to maintain a constant FE_{CO_2}. It was necessary to add carbon dioxide to the gas mixture during hypertension and to reduce the FI_{CO_2} during hypotension. At each point where the MAP was related to the PNA, the MAP had been stable for 20–30 min and the Pa_{CO_2} was close to control values. Relative to human requirements, the dog proved resistant to the effect of vasoactive drugs. After initial pilot observations, the range of change of pressure was to some extent determined by the preparation. After a substantial initial effect, very large doses of the drugs were required to produce further changes in pressure, and the preparation was unstable in terms of maintaining constant blood-gas tensions. To maintain the steady states outlined in the present study, the ranges of the rates of infusion of angiotensin II or SNP were 125–300 μg kg^{-1} min^{-1} and 100–350 μg kg^{-1} min^{-1}, respectively. After the infusion of the vasoactive drug was stopped, MAP was allowed to return to control values. Again, alteration of the FI_{CO_2} was required to maintain Pa_{CO_2} close to control values, and at least 15 min was allowed for stabilization before the Pa_{CO_2}, MAP and PNA were related and measured.

Measurements of PNA referred to in table I are in arbitrary units and are the sum of 10 consecutive peak heights of the integrated signal measured during the relevant period. Since the ventilator was set at the rate of 10 b.p.m. in all preparations, and the phrenic nerve signal remained locked to the ventilator cycle throughout, the measurement of PNA was numerically the ventilator rate–peak height product, that is PNA per min in arbitrary units.

The technique of altering the MAP while

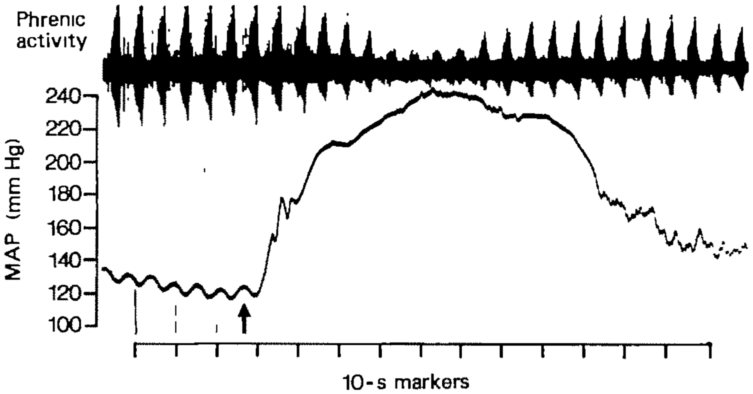

FIG. 1. The effect of a bolus of noradrenaline 500 μg i.v. on mean arterial pressure and phrenic nerve activity.

maintaining normal blood-gas tensions proved difficult and, after pilot experiments, each study was restricted to a single increase or decrease in MAP, with a maximum change which could be readily maintained while the Pa_{CO_2} was re-adjusted to around its control value.

Statistical analysis was performed using paired *t* tests; $P < 0.05$ was regarded as significant.

RESULTS

The effects of bolus injections of NA 500 μg and SNP 10 mg on MAP are illustrated in figures 1 and 2. In response to the injection of NA, there was a rapid increase in MAP (fig. 1) from approximately 120 mm Hg to a maximum of 240 mm Hg within 45 s. However, there was no observable change in PNA until MAP was greater than 200 mm Hg. When MAP reached 220 mm Hg, PNA was virtually abolished and remained so until MAP started to decrease — at which point a change from 240 mm Hg to 220 mm Hg was associated with an immediate increase in PNA to near control values. MAP started to decrease within 10 s of starting the injection of SNP (fig. 2), and the minimum MAP was reached within 25 s. The effect persisted for more than 2 min and was associated with a large increase in PNA. The induced increases and decreases in MAP were associated with alterations

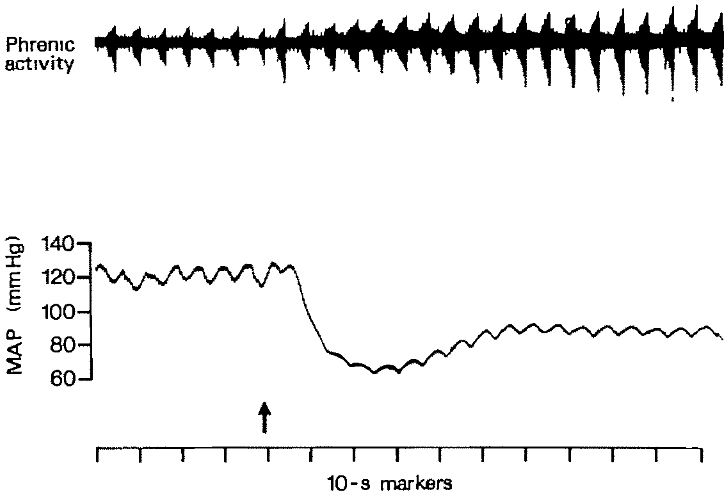

FIG. 2. The effect of a bolus dose of sodium nitroprusside 10 mg i.v. on mean arterial pressure and phrenic nerve activity.

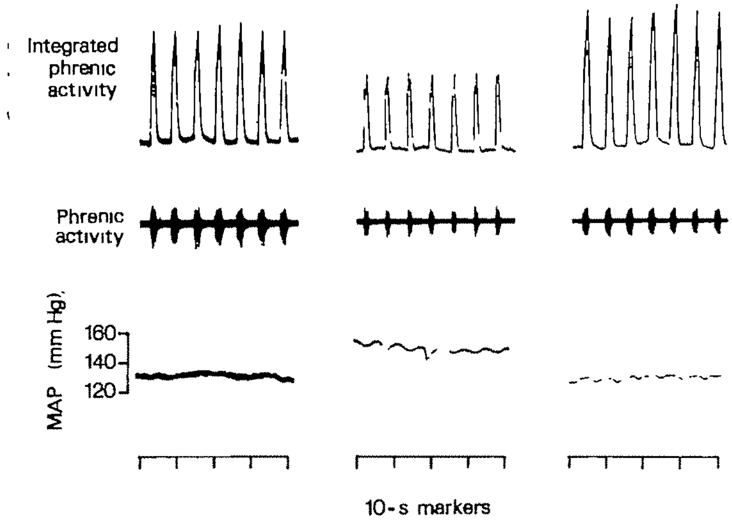

FIG. 3. The changes induced by an infusion of angiotensin II 150 μg kg^{-1} min^{-1} on mean arterial pressure and phrenic nerve activity; each recording during a steady state.

in $F\text{E}_{\text{CO}_2}$ and Pa_{CO_2} which made interpretation of the results of these dynamic studies extremely difficult. Because of the rapid nature of these changes, the $F\text{E}_{\text{CO}_2}$ did not stabilize before the direction of the change in MAP was reversed. $F\text{E}_{\text{CO}_2}$ varied by a maximum of 2% in response to changes in MAP; following bolus doses of SNP, Pa_{CO_2} increased by values varying from 0.5 kPa to 0.9 kPa in different preparations. However, it is impossible to say whether these represent the maximum changes which would have occurred if a steady state had been induced and maintained.

The apparent delay of 5–15 s before a change in MAP caused a change in PNA also presents a problem in interpretation, since accurate measurement of this time was impossible because of the duration of the respiratory cycle which, in these studies, was 6 s so that the observed effect on PNA was always retrospective by at least this period. Thus, the relationship between MAP and PNA cannot be determined from simple studies of this type.

Examples of studies in which the MAP was either increased by AII or decreased by SNP, and in which the blood-gas tensions were maintained constant (by adjusting the $F\text{I}_{\text{CO}_2}$), are shown in figures 3 and 4, respectively. The data obtained from six dogs are summarized in table I and the relevant blood-gas analyses are shown in table II.

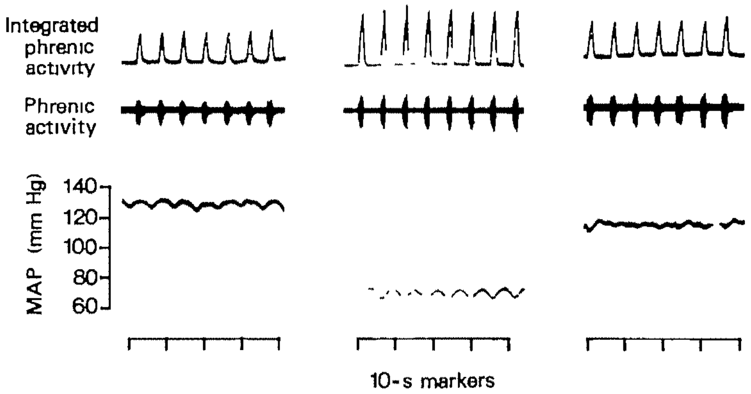

FIG. 4. The changes induced by an infusion of sodium nitroprusside 200 μg kg^{-1} mih^{-1} on mean arterial pressure and phrenic nerve activity; each recording during a steady state.

TABLE I. *Changes in phrenic nerve activity (arbitrary units) associated with changes in mean arterial pressure in six dogs (mean ± SEM)*

	Control (pre)	During changed AP	*P*	Control (post)	*P*
Induced hypertension					
MAP (mm Hg)	114 ± 9	167 ± 10	< 0.02	113 ± 9	< 0.03
PNA	31.0 ± 6.2	22.3 ± 4.8	< 0.01	31.0 ± 6.3	< 0.04
Induced hypotension					
MAP (mm Hg)	128 ± 8.0	82 ± 6.0	< 0.005	124 ± 7.0	< 0.001
PNA	17.2 ± 4.0	21.0 ± 4.2	< 0.01	15.5 ± 3.2	< 0.04

TABLE II. *Changes in mean* Pa_{CO_2} *(kPa), pHa and* Pa_{O_2} *(kPa) during alterations in mean arterial pressure in six dogs (mean ± SEM)*

	Control (pre)	During changed AP	*P*	Control (post)	*P*
Induced hypertension					
Pa_{CO_2}	6.0 ± 0.2	6.1 ± 0.15	ns	6.09 ± 0.19	ns
pHa	7.27 ± 0.02	7.25 ± 0.02	ns	7.21 ± 0.01	ns
Pa_{O_2}	26.7 ± 1.4	30.9 ± 1.9	ns	31.9 ± 1.38	ns
Induced hypotension					
Pa_{CO_2}	6.1 ± 0.23	6.2 ± 0.25	ns	6.3 ± 0.29	ns
pHa	7.22 ± 0.02	7.212 ± 0.02	ns	7.18 ± 0.02	ns
Pa_{O_2}	29.5 ± 1.4	29.7 ± 1.6	ns	30.1 ± 1.9	ns

During induced hypertension a mean increase in MAP of 53 mm Hg, from 114 mm Hg to 167 mm Hg, caused a mean reduction in PNA of 28%. Conversely, a mean reduction in MAP from 128 mm Hg to 82 mm Hg caused a mean increase in PNA of 22% (table I). There were no statistically significant differences in Pa_{CO_2}, Pa_{O_2} or pH at the times when measurements of MAP and PNA were made.

DISCUSSION

This study shows that, in an intact animal with a constant Pa_{CO_2}, minimal peripheral chemoreceptor drive and constant inflation of the lungs, an increase in arterial pressure causes marked respiratory depression, whereas a reduction in pressure stimulates respiration as judged by phrenic nerve activity.

The principal factors which influence central respiratory activity in anaesthetized animals are chemical, for example Pa_{CO_2} and Pa_{O_2} (Duffin, 1971); impulses in afferent nerves from the lungs (Adrian, 1933; Bartoli et al., 1973; Feldman, Cohen and Wolotsky, 1976), the intercostal muscles (Remmers, 1970) and the baroreceptors (Aviado and Schmidt, 1955; Heymans and Neil, 1958; Sampson, Biscoe and Campion, 1968); and other factors such as temperature (Trippenbach and Milic-Emili, 1977) and the depth of anaesthesia. Thus the respiratory neurones in the brain stem receive a variety of interacting inputs and then transmit impulses down at least two descending pathways to the spinal motor neurones which innervate the respiratory muscles (Newsom Davis and Plum, 1972; Mitchell and Berger, 1981; Feldman, McCrimmon and Speck, 1984).

The design of the present study eliminated, as far as possible, all the variables except arterial pressure. It shows that large sustained changes in mean arterial pressure from the set point of the animal will cause substantial changes in efferent phrenic nerve activity which may be taken as a measure of the central respiratory drive to ventilation. Although it is known that the response of the baroreceptors is approximately linear between MAP values of 80 and 180 mm Hg (Pelletier, Clement and Shepherd, 1972) the precise relationship between changes in MAP and PNA would require much more detailed studies than have been described here.

A major problem in the current study was the maintenance of a constant Pa_{CO_2} while mean arterial pressure was varied. It is known that, during induced hypotension, deadspace ventilation increases (Eckenhoff et al., 1963). Thus in the presence of constant ventilation of the lungs an increase in Pa_{CO_2} of the order 0.5–0.9 kPa (as was seen in the present study) could be anticipated. Moreover, the time course of an increase in Pa_{CO_2} is known to be relatively prolonged (Ivanov and Nunn, 1968). Any adjustment of ventilation causes a change in afferent activity from the lungs and, hence, would also be expected to modify the activity of the respiratory centres. These problems were avoided by maintaining tidal volume and respiratory rate constant and producing a high normal Pa_{CO_2} in the control situation by ventilating with carbon dioxide. Thus a constant Pa_{CO_2} could be maintained by the removal of or the addition of carbon dioxide to the inspired gas mixture (without changes in V_T or respiratory rate).

The Pa_{O_2} was maintained above 23 kPa and variations in Pa_{O_2} above this value would not be expected to cause significant changes in central respiratory activity (Duffin, 1971). Cyanide is known to stimulate chemoreceptors; however, recent work has shown that SNP releases very little, if any, cyanide provided it is not exposed to light before infusion (Bisset et al., 1981).

During artificial ventilation, the induction of hypotension will cause an increase in respiratory drive not only as a result of the increase in Pa_{CO_2} with changes in ventilation:perfusion ratios in the lungs, but as a direct result of the decrease in arterial baroreceptor activity, and this appears to be the first work on this aspect of hypotension induced with vasodilators. In a previous study on the effect of noradrenaline on phrenic nerve activity Garcia and Cherniak (1967) avoided the effects of changes in mechanical ventilation on PNA by making observations during apnoeic oxygenation and they counteracted the effect of the increase in Pa_{CO_2} with Tris buffer. They noted a decrease in PNA in response to large increases in arterial pressure. In another study (Grunstein, Derenne and Milic-Emili, 1975) the effect of transient hypertension lasting only 15–30 s (that is, before any changes in Pa_{CO_2} could occur) was observed. Apart from these studies very little has been done on the potential interactions of, for example, the effects of hypoxia and hypotension or PEEP on central respiratory drive in the intact animal. Physiological studies have concentrated on electrical stimulation of the nerves from the various afferent sources or stimulation of isolated groups of physiological receptors (for example by perfusion) and such studies give little idea of the potential magnitude of changes in the intact animal subject to a normal physiological stimulus.

For example, a carotid sinus nerve contains both baroreceptor and chemoreceptor fibres. Low intensity electrical stimulation of the nerve has been shown to inhibit respiratory activity and is, therefore, assumed to cause selective activation of baroreceptor afferents. High intensity stimulation can be stimulatory and is presumed to have activated afferent fibres from the chemoreceptors, since the latter are smaller in size (Biscoe and Millar, 1968; Sampson, Biscoe and Campion, 1968; Biscoe and Sampson, 1970). However, since the thresholds for these fibre groups are not sharply delineated and considerable overlap must exist, it is doubtful if one can stimulate baroreceptor fibres without recruiting at least some chemoreceptor fibres — particularly if an attempt is made to stimulate all the baroreceptor fibres with trains of electrical stimuli. Thus their inhibitory effects may be, at least in part, offset by excitation from chemoreceptor fibres. Moreover, more recent work has suggested just the opposite: namely, that low intensity stimulation of the carotid sinus nerve selectively stimulates chemoreceptor afferents while having a minimal effect on baroreceptor afferents (Eldridge, Millhorn and Waldrop, 1982), and it is difficult to reconcile the findings of these two groups of workers. Thus the effects of electrical stimulation of the carotid sinus nerve may be difficult to interpret and, whatever the relative fibre sizes and stimulus thresholds of baroreceptor and chemoreceptor fibres, it seems unlikely that one group of afferents can be maximally stimulated without involving the other group. Hence, when a physiological stimulus is required, hypertension or hypotension would seem to be more appropriate.

In the present study the measurements of the changes in respiratory activity used the peak height of the rectified integrated signal from the phrenic nerve. In the spontaneously breathing intact animal, PNA occurs during inspiration and the peak height of the integrated PNA signal correlates well with both muscle force output and ventilation (Eldridge, 1971, 1975, 1976). However, in the artificially ventilated animal, with intact vagus nerves, PNA occurs during the expiratory phase (Tang, Maire and Amassian, 1957; Okada and Fox, 1967), being inhibited by the onset of inspiration occasioned by the inflation of the lungs. Whether the PNA represents an "intended tidal volume" is conjectural. The measurements utilized in this study are a representation of central respiratory activity and, during spontaneous and controlled ventilation, are known to be dependent upon temperature in addition to blood-gas tensions (Garcia and Cherniack, 1967; Cohen and Gootman, 1970; Trippenbach and Milic Emili, 1977; Ledlie et al., 1981).

Various factors may interact to affect activity of the peripheral chemoreceptors which may complicate this simple view of the effects of sodium nitroprusside. If the arterial pressure decreases to very low values, afferent activity from the peripheral chemoreceptors will increase (because of the poor perfusion) (Biscoe and Millar, 1968; Duffin, Triscott and Whitwam, 1976). However, since SNP will cause local dilatation of the vessels of the peripheral chemoreceptors, it could, under conditions of normoxia, remove the background chemoreceptor drive (Biscoe, 1971) which normally accounts for 10–15 % of resting ventilation in man and much more during hypoxia (Duffin, 1971). Unlike the condition of hyperoxia in the present study, its local effects in the peripheral chemoreceptors during hypoxia could reduce the drive to ventilation and offset at least in part the effect of the reduced input from the baroreceptors. However, since the Pa_{CO_2} increases during hypotension induced with SNP during fixed mechanical ventilation, it seems likely that the balance of effect will be an increased drive to ventilation. When hypotension occurs during haemorrhage these considerations may not apply, since constriction of the vessels in the peripheral chemoreceptors will occur and both chemoreceptors and baroreceptors will contribute to stimulate ventilation. Miserocchi and Quinn (1980) showed that haemorrhage in spontanously breathing cats anaesthetized with pentobarbitone caused a strong stimulus to ventilation which required the administration of carbon dioxide to maintain a normal Pa_{CO_2} in the presence of hyperventilation — findings which would be in keeping with those of the present study. They stated that a reduction in baroreceptor, and an increase in chemoreceptor, activity were responsible for the observed stimulation of respiration. However, the lowest arterial pressures obtained in their preparations were 60 mm Hg — a value greater than that required to modify chemoreceptor drive resulting from decreased blood flow in cats anaesthetized with inhalation agents (Biscoe and Millar, 1968). Their preparation received 50 % oxygen in nitrogen and in the four out of 30 in which they measured Pa_{O_2} it was "in the range 250 torr". It is possible that local vasoconstriction in the chemoreceptor areas, as suggested above, may have contributed to the perceived increase in ventilation.

These authors reached the general conclusion that vagal afferents affected the frequency of breathing, whereas glossopharyngeal afferents modulated "output" irrespective of the source of these afferents. Thus the results reported here are the first where hypotension was induced with a direct arterial vasodilator during mechanical ventilation and indicate that, as measured by phrenic nerve activity, the dominating issue was determined by output, since the bursts of phrenic activity remained locked to the ventilator cycle throughout.

In conclusion, the effect of the baroreceptors during acute severe hypertension will be to cause respiratory depression which could make the underlying cause worse. A loss of baroreceptor activity during hypotension (induced hypotension or after blood loss) will tend to increase the drive to respiration and contribute to the observed changes in ventilation in such situations.

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CHANGES IN BRAIN SURFACE OXYGEN TENSION DURING PROFOUND HYPOTENSION INDUCED WITH SODIUM NITROPRUSSIDE OR ADENOSINE IN THE SHEEP

J. R. D. LAYCOCK, H. B. COAKHAM, I. A. SILVER AND
F. J. M. WALTERS

SUMMARY

Brain suface oxygen tensions were measured, in sheep (n = 8), with a seven-barrelled mini-electrode polarized by sweep potentials. Mean arterial pressure was reduced to 30 mm Hg with either sodium nitroprusside or adenosine. At this value of mean arterial pressure, oxygen supply to cerebral tissue was impaired. There was no significant difference between the two agents in the degree to which the oxygen supply was reduced.

During neurosurgery, induced hypotension may improve surgical conditions and reduce the likelihood of haemorrhage. However, the decrease in arterial pressure together with disturbances in the cerebral circulation produced by brain retraction may result in variable degrees of cerebral ischaemia and damage to brain substance. Thus it is important to identify those hypotensive agents most likely to preserve cerebral integrity at low perfusion pressures. Of the i.v. agents, sodium nitroprusside (SNP) appears to be superior to trimetaphan in terms of its ability to maintain cortical oxygenation (Maekawa, McDowall and Okuda, 1979) electroencephalographic (EEG) activity (Ishikawa and McDowall, 1981) and ion homeostasis in cerebral tissue (Morris et al., 1983). Recently, adenosine and adenosine triphosphate have been shown to produce rapid, profound hypotension (Fukunaga, Flacke and Bloor, 1982). They may be alternatives to SNP.

If multiple readings of tissue oxygen tension (Pt_{O_2}) are taken with electrodes small enough to resolve the gradients of oxygen tension between individual capillaries, it is possible to build up a picture of tissue oxygenation within the cerebral microcirculation (Lubbers, 1973). This study has used this technique in sheep to compare the effect, on cerebral cortical oxygenation, of profound hypotension to a mean arterial pressure (MAP) of 30 mm Hg with either SNP or adenosine.

MATERIALS AND METHODS

Surgical preparation

Anaesthesia was induced using halothane in nitrous oxide–oxygen (2:1). Laryngoscopy was performed and the trachea intubated. Mechanical ventilation of the lungs was instituted and the volume of ventilation and the inspired oxygen concentration adjusted to maintain an arterial $P\mathrm{CO}_2$ as near 30 mm Hg and arterial $P\mathrm{O}_2$ as near 100 mm Hg as possible. Hartmann's solution was infused at $5\ \mathrm{ml\ kg^{-1}\ h^{-1}}$, and internal jugular and femoral arterial cannulae inserted. Arterial and central venous pressures were monitored continously (Statham P23 pressure transducers) and recorded on a Grass model 5D polygraph. End-tidal carbon dioxide was measured with a Beckmann LB2 CO_2 analyser, and samples of arterial blood were taken regularly for analysis on an ABL 2 blood-gas analyser (Radiometer, Copenhagen).

A 2-cm diameter fronto–parietal craniectomy was performed, the dura reflected, and the defect in the skull covered with plastic sheeting (Op-Site, Smith and Nephew Ltd) during periods when no

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J. R. D. LAYCOCK,* F.F.A.R.C.S., F. J. M. WALTERS, F.F.A.R.C.S, (Department of Anaesthetics); H. B. COAKHAM, F.R.C.S. (Department of Neurosurgery); Frenchay Hospital, Bristol. I. A. SILVER, M.R.C.V.S., Department of Pathology, University Medical School, Bristol.

* Present address: Department of Anaesthetics, Royal Victoria Hospital, 687 Pine Avenue West, Room H522, Montreal, Canada H3A 1A1.

oxygen tensions (Pt_{O_2}) were being measured. Brain surface temperature was monitored by means of a 2-mm bead thermistor (RS Components Ltd, U.K.). Following surgical preparation, the inspired halothane concentration was reduced to 0.5% and the animal allowed to stabilize for 45 min before proceeding with the investigation. A total of eight animals was used for both control readings and the measurement of Pt_{O_2} during arterial hypotension.

Decreases in arterial pressure

After the surgical preparation and the period of stabilization, a series of control readings was obtained from each animal. In four sheep, hypotension was then induced to an MAP of 30 mm Hg with adenosine infused at a rate of 2.5 mg kg^{-1} min^{-1} initially. The rate was adjusted depending on the response observed. On attaining the required arterial pressure, an arterial sample was taken for blood-gas analysis, and measurements of Pt_{O_2} made over 15 min. After the period of hypotension the arterial pressure was allowed to recover while the oxgyen electrode was recalibrated, and 15 min elapsed before hypotension was again induced on two more occasions. In the four remaining animals, SNP was used to decrease MAP to 30 mm Hg (initial infusion rate of 10 µg kg^{-1} min^{-1}). Estimations of Pt_{O_2} were performed as described above.

Determination of brain oxygen tensions

The design and operation of the seven-barrelled oxygen electrode used intermittent sweep as opposed to continuous polarography (Laycock et al., 1984). The electrode itself was of a standard membrane-covered design (Clark, 1956), and consisted of seven 25-µm platinum wires fused into glass and supported in a stainless steel casing. At the working surface of the probe the platinum wires were ground to a plane surface so that the electrode could measure oxygen tensions at tissue surfaces. The assembly was first calibrated in solutions of physiological saline equilibrated with nitrogen and 10% oxygen in Adams tonometers. These solutions were maintained at the temperature recorded at the cortical surface by a circulating water bath. The electrode assembly was then applied to the cortical surface by means of a counterbalanced arm modified from one previously described for use with a single oxygen probe (Powell et al., 1983). This arm allowed the electrode to float on the surface of the brain without exerting more than 0.5 g cm^{-1} pressure on the substance of the brain, while the probe was manoeuvered randomly across small areas of the exposed cortex by adjustments to the counterbalancing mechanism. After measurements in the animal, the electrode was returned to the calibrating solutions and recalibration performed.

Analysis of results

For each steady state period (that is control, or during hypotension with adenosine or SNP), the Pt_{O_2} values obtained were pooled and then plotted in histogram form using a Hewlett–Packard 9810A calculator/plotter. Detection of statistically significant differences between the histograms was made by means of the Mann–Whitney *U* test. The results from blood-gas analysis were compared using Student's *t* test.

RESULTS

Mean arterial and venous pressures and the results from blood-gas analysis during the different steady states are shown in table I. Arterial oxygen tension decreased during hypotension, but the difference did not achieve significance. Frequency histograms for Pt_{O_2} are shown in figures 1, 2 and 3, and the salient features of each histogram summarized in table II. During normotension, 3245 control cortical Pt_{O_2} readings were obtained, when these were plotted in histogram form (fig. 1) the modal value was in the range 3.9–4.6 kPa, but with a wide range of observed values for Pt_{O_2},

TABLE I. *Mean values (SEM) for MAP (mm Hg), CVP (mm Hg), arterial* P_{O_2} *(kPa),* P_{CO_2} *(kPa) and pH, during control conditions at normotension, and during hypotension to 30 mm Hg with either SNP or adenosine.* *$P < 0.05$; **$P < 0.001$

	MAP	CVP	P_{O_2}	P_{CO_2}	pH
Control	87 (7.1)	2.1 (0.61)	14.5 (1.5)	4.1 (0.51)	7.32 (0.032)
SNP	30 (2.1)**	0.6 (0.30)*	11.8 (0.5)	4.2 (0.20)	7.32 (0.010)
Adenosine	32 (1.8)**	0.8 (0.55)	12.0 (1.1)	3.8 (0.47)	7.26 (0.035)

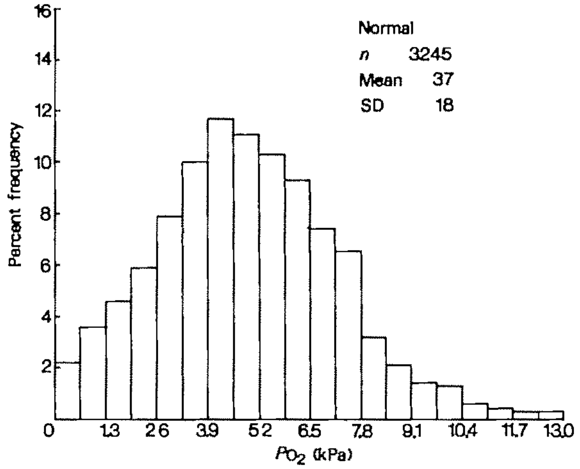

FIG. 1. Frequency histogram of brain surface oxygen tensions during normotension. $n = 8$.

TABLE II. *Mean* Pt_{O_2} *(kPa), standard deviation, model* Pt_{O_2} *and the percentage of the total values less than 0.65 kPa during hypotension to an MAP of 30 mm Hg with SNP or adenosine*

	Mean Pt_{O_2}	SD	Modal Pt_{O_2}	% Freq. < 0.65 kPa
Control	4.9	2.4	3.9–4.6	2.2
SNP	3.7	3.2	2.0–2.6	5.1
Adenosine	3.4	2.2	2.0–2.6	8.6

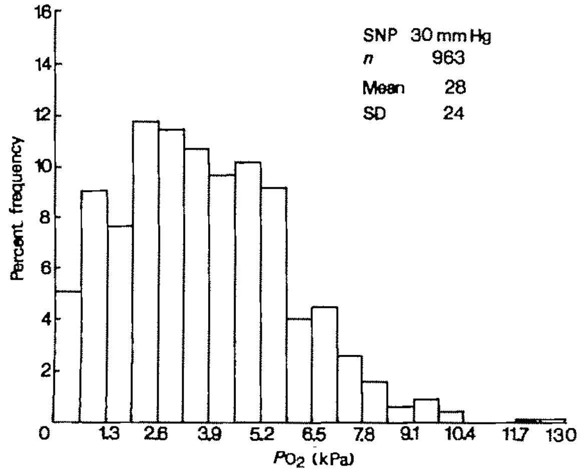

FIG. 2. Frequency histogram of brain surface oxygen tensions during hypotension to an MAP of 30 mm Hg with SNP. $n = 4$.

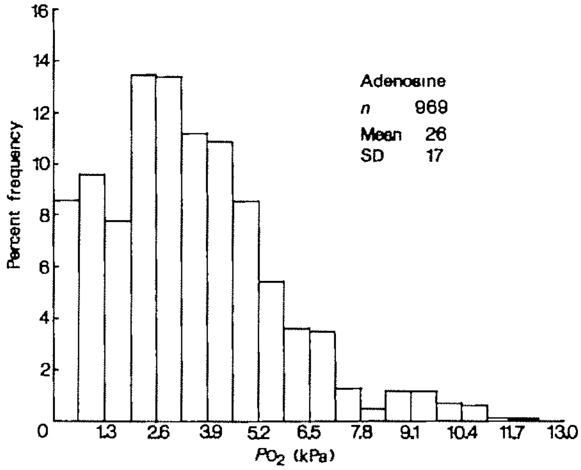

FIG. 3. Frequency histogram of brain surface oxygen tensions during hypotension to an MAP of 30 mm Hg with adenosine. $n = 4$.

some areas exhibiting tensions near that of arterial blood, and some areas displaying tensions very near zero. During hypotension to an MAP of 30 mm Hg with SNP and adenosine (figs 2 and 3) there were significant shifts of the oxygen histograms to the left ($P < 0.01$) when compared with control. There was no significant difference between the histograms obtained during the infusion of SNP or adenosine. The frequency at which extremely low Pt_{O_2} values (between 0 and 0.65 kPa) occurred increased from 2.2% during control conditions to 5.1% when SNP, and to 8.6% when adenosine, was being infused.

DISCUSSION

SNP is not the ideal agent with which to produce hypotension because of effects on intracranial pressure (Turner et al., 1977; Cottrell et al., 1978), activation of the renin–angiotensin system (Zubrow et al., 1983), tachyphylaxis (Tinker and Michenfelder, 1976) and the occurrence of rebound hypertension (Packer et al., 1979). Although ATP (which has a similar mode of action as adenosine) produces increases in intracranial pressure, especially in the presence of reduced intracranial compliance (Van Aken et al., 1984), the absence of tachycardia, tachyphylaxis and rebound hypertension seen with ATP and adenosine (Fukunaga, Flacker and Bloor, 1982) has led to interest in their use as agents for the induction of profound hypotension. Studies in the rat (Hoffman et al., 1982) and the dog (Lagerkranser et al., 1984) have confirmed these advantageous properties of ATP and adenosine, and their hypotensive effects have been studied during surgery in man (Fukunaga, Ikeda and Matsuda, 1982; Sollevi et al., 1984). All these studies have generally been performed with reductions in MAP to values of 40–80 mm Hg.

The purpose of this study was to compare the effect on cortical oxygenation of profound hypotension, with adenosine or SNP, with values of MAP where disturbances in cortical electrical activity or ion homeostasis are seen. This was achieved by measurement of multiple cortical oxygen tensions with small electrodes.

The factors which influence oxygen tension at any given point in the tissues are complex and include the pattern of the capillary network, the oxygen tension at the capillary wall, the rate of oxygen uptake by the tissues, the diffusion coefficient for oxygen within the tissues and the distance over which oxygen has to be transported (Krogh, 1919). The oxygen tension at the capillary wall will, in turn, depend on the flow of blood within the capillaries and the capacity of blood flowing within the capillaries for transporting oxygen. However, by taking multiple readings of Pt_{O_2} with probes small enough to resolve the oxygen gradients between capillaries it is possible to describe an "oxygen tension field" by constructing histograms of tissue oxygenation. This will give direct information about the adequacy of the microcirculation and the supply of oxygen to cerebral tissues. A further advantage of this technique is that, unlike measurements of local cerebral blood flow, it will give direct information about the homogeneity of capillary flow.

Using the technique of sweep potential polarography with 25-µm electrodes we found histograms of brain surface Pt_{O_2} similar to those obtained previously in guineapigs (Lubbers, 1973) and cats (Maekawa, McDowall and Okuda, 1979). Despite this, the anaesthetic technique which was used in the present investigations may have interfered with the results obtained in two ways. Electrochemical reduction of halothane is known to occur at the surface of platinum electrodes at −700 mV, so interfering with the measured oxygen current. This effect is much less marked with low halothane concentrations (Crockard et al., 1976; Brooks et al., 1982). For this reason the inspired halothane concentration was reduced and the sheep stabilized with 0.5% halothane for a period of 45 min after the surgical preparation before Pt_{O_2} readings were taken. Any effect exerted by halothane would have been similar at all times as the inspired concentration was always held at 0.5%. Nitrous oxide within the tissues would not have interfered with the results as electrochemical reduction of this substance does not occur at −700 mV with intermittently polarized electrodes (Brooks et al., 1982).

Second, halothane is a cerebral vasodilator, and produces a dose-dependent increase in cerebral blood flow (CBF). However, CBF does adjust and return to near normal values approximately 90 min after the start of halothane administration (Albrecht, Miletich and Madala, 1983). Halothane also impairs cerebral autoregulation in response to drug-induced hypotension (Fitch et al., 1976), although again this effect is dose-dependent and far less marked at low inspired halothane concentrations.

The results presented here show that, at an MAP of 30 mm Hg in the sheep, cortical oxygenation is impaired to the same extent during SNP and adenosine administration. This is consistent with studies which have shown that adenosine (like SNP) is a cerebral vasodilator (Forrester et al., 1979), and that the cerebral energy state is impaired to a similar extent by both agents (Newberg, Milde and Michenfelder, 1985). On the other hand, there is some evidence that cerebral ion homeostasis may be less disturbed during ATP as opposed to SNP hypotension (Heuser, Guggenberger and Morris, 1984).

The results obtained during the administration of SNP exhibit differences from those obtained in similar experiments in the cat (Maekawa, McDowall and Okuda, 1979). In cats no disturbance in cortical oxygenation was detected when SNP was used to produce reductions in MAP to either 40 or 30 mm Hg. Apart from differences in the behaviour of the microcirculation at these low pressures in the two different species, a possible explanation is that, in cats, the arterial oxygen tension was greater (20 kPa), so providing a steeper gradient for oxygen diffusion to the tissues. Furthermore, in the sheep, moderate hypocapnia was used, and the resultant cerebral vasoconstriction may have enhanced the effects of profound hypotension on cerebral Pt_{O_2}.

It is concluded that, at very low perfusion pressures, similar impairment in cortical oxygenation occurs with the use of either SNP or adenosine.

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IN VITRO MUSCLE CONTRACTURES INDUCED BY HALOTHANE AND SUXAMETHONIUM

I: The Rat Diaphragm

J. E. FLETCHER AND H. ROSENBERG

SUMMARY

The rat diaphragm was used as an in vitro *model for studies of contractures synergistically-induced by halothane and suxamethonium. The effects of three agents reported to inhibit phospholipase A_2 activity (quinacrine, spermine and indomethacin), tubocurarine and dantrolene were examined on these contractures. Contractures induced by 1% halothane (0.26 ± 0.02 g) (mean ± SEM) were increased (0.60 ± 0.04 g) if suxamethonium 50 mmol litre^{-1} was also in the bathing medium. Suxamethonium-induced contractures (0.22 ± 0.03 g) were also enhanced when halothane was present (0.51 ± 0.03 g). Spermine, indomethacin and dantrolene antagonized both halothane- and suxamethonium-induced contractures. Quinacrine potentiated contractures induced by either halothane or suxamethonium. Contractures induced by suxamethonium were antagonized by tubocurarine; however, contractures induced by halothane were not antagonized by tubocurarine. These results suggest that free fatty acids may be involved in contractures induced synergistically by halothane and suxamethonium. Different mechanisms are involved in the induction of contractures by suxamethonium than by halothane.*

Malignant hyperthermia (MH) is a potentially fatal syndrome triggered by the potent volatile general anaesthetic agents and suxamethonium. Susceptibility to MH is diagnosed by the contracture response of skeletal muscle to halothane or caffeine, or both (Kalow et al., 1970; Moulds and Denborough, 1974; Rosenberg and Reed, 1983). The porcine stress syndrome resembles human MH and can also be triggered by the potent volatile general anaesthetic agents and suxamethonium (Gronert, 1980). Muscle strips from pigs susceptible to the porcine stress syndrome also exhibit a lower contracture threshold to halothane than do those from control pigs. The mechanisms underlying halothane-induced contractures of muscle are poorly understood.

A synergism exists between suxamethonium and halothane that has been observed clinically (Tammisto and Airaksinen, 1966; Innes and Strømme, 1973; Schwartz, Rockoff and Koka, 1984) and *in vitro* (Fletcher and Rosenberg, 1985, 1986). When examined *in vitro*, this interaction appears to require the liberation of fatty acids by suxamethonium (Fletcher and Rosenberg, 1986).

The access to human and pig skeletal muscle is limited. Obtaining a large number (8–12) of preparations without cut fibre ends from the same muscle is difficult with pigs and impossible in man. Also, the thickness of preparations of human and pig skeletal muscle fibres makes them less than ideal for pharmacological and physiological studies of contracture. The rat diaphragm is relatively thin, allowing a much larger percentage of the fibres to be oxygenated and exposed to the drugs introduced to the bath. The purpose of the present study was to develop a mammalian (small rodent) model system in which halothane-induced contractures and the interaction between suxamethonium and halothane could be conveniently examined *in vitro*. In this study agents known to antagonize phospholipase A_2 (PLA_2) activity were

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Jeffrey E. Fletcher, ph.d.; Henry Rosenberg, m.d.; The Laboratory for the Study of Malignant Hyperthermia, Department of Anesthesiology, Hahnemann University, Philadelphia, PA, U.S.A. 19102.

used to determine whether PLA_2 activity could be involved in halothane-induced contractures of the rat diaphragm. Dantrolene, the drug of choice for epidoses of MH, was used, as dantrolene has been shown previously to block halothane-induced contractures in muscle strips from other species. Finally, the effects of tubocurarine were examined on the synergistic induction of contractures by halothane and suxamethonium (Gronert, 1980).

MATERIALS AND METHODS

Male Sprague–Dawley rats (200–400 g) were decapitated and the diaphragm was removed. Muscle strips (about 4 × 8 × 0.5 mm) were prepared by cutting the diaphragm parallel to the direction of the fibres from the rib section to the central tendon. Dissection was undertaken at 25 °C in Krebs solution composed of (mmol $litre^{-1}$): NaCl 118, KCl 3.4, $MgSO_4$ 0.8, KH_2PO_4 1.2, glucose 11.1, $NaHCO_3$ 25.0 and $CaCl_2$ 2.5, and pH adjusted to 7.4. Usually, eight to 12 muscle strips could be prepared from a single diaphragm. Preparations were mounted in a tissue bath containing Krebs solution at 37 °C and bubbled with oxygen–carbon dioxide (95:5). The rib section of each strip was tied to a fixed position stimulating electrode and the central tendon connected to a force transducer. The muscle strips were adjusted to an initial resting tension of 1 g and directly stimulated at 0.2 Hz with supramaximal voltage pulses of 2 ms duration. Only preparations maintaining a stable resting tension for 30 min were used subsequently. Following the 30-min equilibration period, 1 % halothane was added to the gas phase. The time of exposure to halothane alone was 5 min. Suxamethonium was then added to the bath and the maximum contracture within 5 min to both agents recorded. In some experiments suxamethonium was added to the bath 5 min before halothane. When interaction studies were carried out with suxamethonium and halothane, those strips exhibiting a contracture greater than 0.5 g to the first agent added (except to 3 % halothane) were not used further in the study. This resulted in rejection of about 10 % of the total number of strips tested. These strips were eliminated because, on occasions, the resting tension of the preparation would not recover from the effect of the administration of the first drug before it was time to add the second agent. The results are expressed in terms of numbers of rats used. For each rat the average response of one to 12 strips was treated as a single value. When used, tubocurarine, spermine, indomethacin, quinacrine or dantrolene was added to the bath 2 min before suxamethonium or halothane. Krebs solution was the solvent for all drugs in the study, as solvents such as ethanol potentiate contractures induced by halothane (unpublished observations). The pH was adjusted to 7.4 for each solution of drug. Solutions of dantrolene and indomethacin were sonicated before use. Indomethacin and tubocurarine were not completely soluble at 1 and 50 mmol $litre^{-1}$, respectively. The halothane concentration in the gas phase was confirmed by gas chromatography, using an OV-101 (3 %) Chrom-W-HP 100–120 mesh (Perkin–Elmer) column.

Indomethacin, spermine, quinacrine, suxamethonium and tubocurarine were purchased from Sigma Chemical Co. (St Louis, MO). Caffeine was obtained from Eastman (Rochester, NY) and halothane from Ayerst (New York, NY). Dantrolene sodium was a gift of Norwich Pharmaceutical Co. (Norwich, NY).

The unpaired data in tables I and IV were each analysed using a one-way analysis of variance followed by Duncan's multiple range test. Significance was tested at the $P < 0.05$ level. The data in tables II and III were analysed using two-sided paired *t* tests.

RESULTS

The typical responses of the strips of rat diaphragm muscle to halothane and suxamethonium alone, or in combination, are demonstrated in figure 1. Preparations exhibited significantly greater contractures to either halothane or suxamethonium if the other agent was also present in the bath, than to either agent alone. The diaphragms from some rats exhibited greater contractures to 1 % halothane or suxamethonium 50 mmol $litre^{-1}$ when administered alone than did those from other rats (unpublished observations). Some young rats (about 6 weeks of age) exhibited contractures to halothane that exceeded 1.2 g. Currently, we believe the response to these agents may vary with season and age.

Halothane 1 % elicited relatively small contractures from the rat diaphragm preparation (table I). The size of the contractures was significantly increased when the concentration of halothane was increased to 3 % (table I). Contractures induced by 1 % halothane in preparations pre-exposed to suxamethonium became increasingly

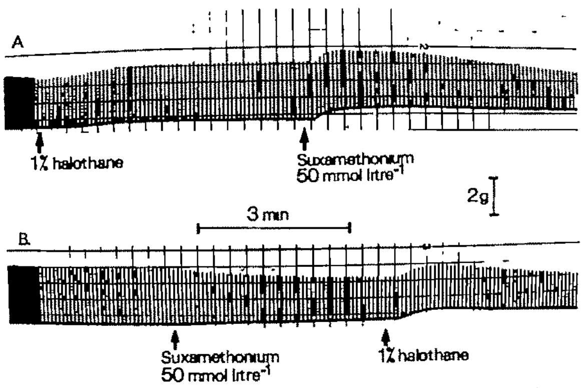

FIG. 1. Effects of 1% halothane and suxamethonium 50 mmol litre^{-1} on directly stimulated muscle strips isolated from the rat diaphragm. Tracings A and B are of the same muscle preparation. After the suxamethonium response (contracture) in tracing A halothane was discontinued, the preparation was washed and re-equilibrated for 30 min. Tracing B shows the drug additions following the 30 min equilibration. Notice that suxamethonium and halothane induced significant contractures only if the other agent was present.

greater in magnitude as the suxamethonium concentration was increased in the range of 1–50 mmol litre^{-1} (table I). There was no response to suxamethonium at the concentrations of 1 or 10 mmol litre^{-1} in the absence or presence of 1% halothane. Contractures induced by suxamethonium 50 mmol litre^{-1} were not significantly different from those induced by 1% halothane. Suxamethonium 50 mmol litre^{-1}-induced contractures were increased significantly when preparations were preincubated with 1% halothane (table I). Contractures induced by suxamethonium 50 mmol litre^{-1} in the presence of halothane did not increase significantly when the halothane concentration was increased to 3%. In contrast, halothane-induced contractures in the presence of suxamethonium 50 mmol litre^{-1} were greater at a halothane concentration of 3% than at 1% (table I).

The effects of various antagonists were examined with 1% halothane and suxamethonium 50 mmol litre^{-1}. Results obtained with tubocurarine are shown in table II. Tubocurarine did not induce significant contractures in the rat diaphragm, even at a concentration of 50 mmol litre^{-1}. Contractures induced by suxamethonium in the presence of halothane were antagonized by tubocurarine (table II). However, contractures induced by halothane in the presence of suxamethonium were not antagonized by tubocurarine (table III). Dantrolene antagonized the contractures induced by either suxamethonium or halothane (tables II and III, respectively).

Two PLA$_2$ inhibitors, spermine and indomethacin, antagonized the interaction response to either suxamethonium (table II) or halothane (table III). A third PLA$_2$ inhibitor, quinacrine, did not antagonize suxamethonium-induced contractures in preparations pre-exposed to halothane (table IV). In addition, quinacrine did not antagonize halothane-induced contractures in

TABLE I. *Interaction between halothane and suxamethonium on contractures induced in the rat diaphragm. Suxamethonium and halothane were added within 5 min of each other. The values represent the maximum contracture within 5 min of addition of the second agent. Significant differences* ($P < 0.05$) *when compared with: *1% halothane alone; †Suxamethonium 50 mmol litre^{-1} alone; ‡Suxamethonium 1 mmol litre^{-1} followed by 1% halothane; §Suxamethonium 10 mmol litre^{-1} followed by 1% halothane; ¶Suxamethonium 50 mmol litre^{-1} followed by 1% halothane; ** 3% halothane alone*

Sequence of agent addition			
First	Second	Contracture (g) (mean ± SEM)	*n*
None	1% Halothane	0.26 ± 0.02	24
Suxamethonium (1 mmol litre^{-1})	1% Halothane	0.30 ± 0.06	6
Suxamethonium (10 mmol litre^{-1})	1% Halothane	0.45 ± 0.08*‡	10
Suxamethonium (50 mmol litre^{-1})	1% Halothane	0.60 ± 0.04*‡§	19
None	Suxamethonium 1 mmol litre^{-1}	0.00 ± 0.0†	6
None	Suxamethonium 10 mmol litre^{-1}	0.01 ± 0.01†	10
None	Suxamethonium 50 mmol litre^{-1}	0.22 ± 0.03	19
Halothane (1%)	Suxamethonium 1 mmol litre^{-1}	0.00 ± 0.00†	6
Halothane (1%)	Suxamethonium 10 mmol litre^{-1}	0.05 ± 0.03†	10
Halothane (1%)	Suxamethonium 50 mmol litre^{-1}	0.51 ± 0.03†	20
None	3% Halothane	0.55 ± 0.07*	4
Suxamethonium (50 mmol litre^{-1})	3% Halothane	0.80 ± 0.16*¶**	4
Halothane (3%)	Suxamethonium 50 mmol litre^{-1}	0.54 ± 0.02†	4

TABLE II. *Effects of phospholipase A_2 inhibitors, tubocurarine and dantrolene on suxamethonium 50 mmol litre^{-1}-induced contractures in the presence of 1% halothane. Suxamethonium was added 5 min after halothane. Inhibitors were added to the bath 2 min before the addition of halothane. The response shown is the mean SEM for the indicated number of animals. Significant differences when compared with absence of inhibitor:* *$P < 0.05$; ***$P < 0.001$

		Response to suxamethonium: Contracture (g)	
Agent	n	(−Inhib.)	(+Inhib.)
Spermine 10 mmol litre^{-1}	6	0.46±0.06	0.32±0.05***
Indomethacin 1 mmol litre^{-1}	4	0.55±0.04	0.08±0.05***
Tubocurarine 50 mmol litre^{-1}	8	0.50±0.03	0.34±0.05*
Dantrolene 1 µmol litre^{-1}	3	0.51±0.02	0.10±0.06*

TABLE III. *Effects of phospholipase A_2 inhibitors, tubocurarine and dantrolene on 1% halothane-induced contractures in the presence of suxamethonium 50 mmol litre^{-1}. Halothane was added 5 min after suxamethonium. Inhibitors were added to the bath 2 min before the addition of suxamethonium. The response shown is the mean±SEM for the indicated number of animals. Significant differences when compared with suxamethonium then halothane alone:* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

		Response to halothane: Contracture (g)	
Agent	n	(−Inhib.)	(+Inhib.)
Spermine 10 mmol litre^{-1}	5	0.56±0.06	0.31±0.30*
Indomethacin 1 mmol litre^{-1}	8	0.49±0.05	0.19±0.04***
Tubocurarine 50 mmol litre^{-1}	8	0.58±0.06	0.55±0.07
Dantrolene 1 µmol litre^{-1}	6	0.52±0.07	0.20±0.04**

TABLE IV. *Effects of quinacrine 100 µmol litre^{-1} on 1% halothane- and suxamethonium 50 mmol litre^{-1}-induced contractures. Quinacrine was added to the bath 2 min before the addition of halothane or suxamethonium. Halothane and suxamethonium were added within 5 min of each other. The response shown is the mean ± SEM for each of 12 animals. Significant differences* ($P < 0.05$) *when compared with:* **suxamethonium alone;* †*halothane alone;* ‡*quinacrine followed by halothane*

Sequence of agent addition			
First	Second	Third	Contracture (g)
None	None	Halothane	0.33±0.04*‡
None	None	Suxamethonium	0.11±0.02‡
None	None	Quinacrine	0.08±0.03‡
None	Quinacrine	Halothane	0.82±0.12*†
None	Quinacrine	Suxamethonium	0.55±0.09*†‡
None	Halothane	Suxamethonium	0.45±0.04*‡
None	Suxamethonium	Halothane	0.53±0.05*†‡
Quinacrine	Halothane	Suxamethonium	0.48±0.05*†
Quinacrine	Suxamethonium	Halothane	0.49±0.05*†

preparations pre-exposed to suxamethonium (table IV). The response to 1% halothane following the addition of quinacrine to the bath (no suxamethonium present) was much greater than in the absence of quinacrine (table IV). Quinacrine also enhanced suxamethonium-induced contractures in the absence of halothane in the bath (table IV).

DISCUSSION

Suxamethonium and halothane act synergistically to induce contractures in directly stimulated muscle strips isolated from the rat diaphragm. This interaction is similar to that observed using preparations isolated from biopsies of human skeletal muscle (Fletcher and Rosenberg, 1985, 1986). This interaction between halothane and suxamethonium does not appear to be simply additive, as the order in which the drugs were added determined the degree of response to the second agent. For example, the response to suxamethonium 50 mmol litre^{-1} was not significantly increased in preparations pre-incubated with halothane when the halothane concentration was increased from 1 to 3%. In contrast, the response to halothane in preparations pre-exposed to suxamethonium 50 mmol litre^{-1} was increased when the concentration of halothane was increased from 1 to 3%. Also, there was essentially no response to suxamethonium 10 mmol litre^{-1} in the presence of 1% halothane. When the order in which the agents were added to the bath was reversed, 1% halothane-induced contractures were increased significantly in the presence of suxamethonium 10 mmol litre^{-1}. Thus, separate mechanisms may be involved in the response to each of the agents. Further evidence for separate mechanisms in halothane- and suxamethonium-induced contractures was the observation that tubocurarine antagonized suxamethonium-induced contractures, but not those induced by halothane. These results are in agreement with the clinical situation in regard to MH: that is, tubocurarine can prevent suxamethonium-induced MH, but not halothane-induced MH (Harrison, 1971; Hall, Lucke and Lister, 1976). These results may not be mediated at the endplate, as such high concentrations of suxamethonium and tubocurarine are required, respectively, to induce or antagonize contractures.

The results of the present study, using indomethacin and spermine, suggest that PLA$_2$ activity may be involved in halothane and suxamethonium-induced contractures in the rat diaphragm. The results obtained with quinacrine on the diaphragm preparation are more complex. Studies using human muscle have demonstrated that quinacrine can block halothane and suxamethonium-induced contractures (Fletcher and Rosenberg, 1986). A recent report suggests that the increased specific activity in pigs susceptible to the porcine stress syndrome may result from a greater concentration of calmodulin (Cheah, 1984), which would stimulate calmodulin-dependent PLA$_2$. Although we do not understand the difference in response between rat and human preparations, one possible explanation is that PLA$_2$ activity of the rat diaphragm may not be calmodulin-dependent. Alternatively, an action of quinacrine other than the inhibition of PLA$_2$ may account for the potentiation of the contractures induced by halothane and suxamethonium. Regardless of the reason for this discrepancy, the difference between human and rat preparations in the action of quinacrine can be used to understand better the role of lipolysis in the induction of contractures. Although PLA$_2$ activity is presumed to be the source of fatty acids, it is premature to eliminate other lipolytic enzymes including PLA$_1$, triglyceride lipase, diglyceride lipase, and so on.

Dantrolene is known to block Ca^{2+} release from the sarcoplasmic reticulum (Martonosi, 1984). In view of the present study, dantrolene could be a potent PLA$_2$ inhibitor. The inhibition of PLA$_2$ activity could be either direct or indirect. An example of an indirect mechanism would be the blocking of Ca^{2+} availability to the Ca^{2+}-dependent PLA$_2$ enzyme. Alternatively, dantrolene may physiologically antagonize the effects of the unsaturated fatty acids on Ca^{2+} regulation.

In conclusion, muscle strips isolated from the rat diaphragm are useful in investigations of drug-induced contractures. The fibre strips are thin and are mostly uncut—highly desirable features when compared with the human and pig fibre bundles used frequently in such studies. The interaction between halothane and suxamethonium in the present studies appears similar to that observed using human skeletal muscle, except for the interactions of halothane and suxamethonium with quinacrine. In addition, the present study demonstrates that suxamethonium and halothane induce contractures through different mechanisms. These studies support a role for fatty acids in contractures synergistically induced by halothane and suxamethonium.

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IN VITRO MUSCLE CONTRACTURES INDUCED BY HALOTHANE AND SUXAMETHONIUM

II: Human Skeletal Muscle from Normal and Malignant Hyperthermia Susceptible Patients

J. E. FLETCHER AND H. ROSENBERG

SUMMARY

The role of lipolysis in halothone-induced contractures of human skeletal muscle was examined using three inhibitors of phospholipase A_2 (PLA_2) activity (quinacrine, spermine and indomethacin) and exogenously administered PLA_2. In addition, we examined the effects of the same PLA_2 inhibitors on contractures induced by halothane in combination with suxamethonium. The studies were conducted on directly stimulated muscle strips isolated from biopsies from patients diagnosed as MH susceptible, or not susceptible, by the halothane contracture test. The liberation of fatty acids from skeletal muscle homogenates was examined to determine whether PLA_2 activity might be increased in MH susceptible patients. The three PLA_2 inhibitors antagonized halothane-induced contractures of muscle from MH susceptible patients as well as induction of contractures by suxamethonium and halothane. Pre-exposing preparations that were previously unresponsive to halothane to bee venom PLA_2 caused the muscle strips to respond with contractures upon subsequent challenge with halothane, but not with suxamethonium. Free fatty acid production during an in vitro *incubation of skeletal muscle homogenates was greater in preparations from MH susceptible patients than in those from patients who were not susceptible. These results suggest that excess liberation of fatty acids may be involved in halothane-induced contractures of muscle from MH susceptible individuals, in the synergism observed between halothane and suxamethonium, and in human MH.*

Malignant hyperthermia (MH) is a potentially fatal genetic disorder associated with the use of halogenated volatile anaesthetic agents and suxamethonium (Gronert, 1980). The porcine stress syndrome (PSS) appears very closely related to human MH and can be triggered in certain strains by stress, volatile anaesthetics or suxamethonium (Gronert, 1980). The most widely used means by which MH may be diagnosed involve a muscle biopsy, and the *in vitro* exposure of the isolated muscle strips to halothane and caffeine. Muscle strips from patients susceptible to MH have a lower contracture threshold when exposed to halothane or caffeine than do those from patients with no susceptibility to MH (Kalow et al., 1970; Moulds and Denborough, 1974; Rosenberg and Reed, 1983).

Phospholipase A_2 (PLA_2; EC 3.1.1.4) activity is increased in skeletal muscle from pigs susceptible to the porcine stress syndrome (Cheah and Cheah, 1981a, b). We wished to examine whether the liberation of fatty acids plays a role in the induction of contractures in skeletal muscle by halothane. To determine whether lipolytic activity is involved in the greater sensitivity to halothane of muscle from MH susceptible patients, we examined the effects of three inhibitors of PLA_2 activity (quinacrine, spermine and indomethacin) on halothane-induced contractures.

A clinical synergism between halothane and suxamethonium has been noted. One in 100 children anaesthetized with halothane and given

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JEFFREY E. FLETCHER, PH.D.; HENRY ROSENBERG, M.D.; The Laboratory for the Study of Malignant Hyperthermia, Department of Anesthesiology, Hahnemann University, Philadelphia, PA, U.S.A. 19102.

suxamethonium develops rigidity of the masseter muscles (Schwartz, Rockoff and Koka, 1984). Masseter rigidity is a frequent premonitory sign of MH (Rosenberg and Reed, 1983). In addition, halothane and suxamethonium act synergistically in regard to the increases in serum creatine phosphokinase concentration (Tammisto and Airaksinen, 1966; Innes and Strømme, 1973), and myoglobinaemia (Harrington, Ford and Striker, 1984). Since suxamethonium stimulates PLA_2 activity in skeletal muscle (Olthoff, Kunze and Kries, 1973), we examined the role of PLA_2 activity in the synergistic induction of contractures observed with suxamethonium and halothane in an *in vitro* skeletal muscle preparation (Fletcher and Rosenberg, 1985).

In the susceptible pig, the production of free fatty acid during *in vitro* incubation of a mitochondrial fraction isolated from skeletal muscle is greater than that observed in control preparations (Cheah and Cheah, 1981b). Therefore, in the present study the liberation of fatty acids was determined during an *in vitro* incubation of muscle homogenates in order to determine if lipolytic activity is also increased in muscle from MH susceptible patients.

Preliminary results from this study have been published previously (Fletcher, Rosenberg and Hilf, 1984a).

MATERIALS AND METHODS

Materials

Indomethacin, spermine, quinacrine, bee venom PLA_2 and suxamethonium were purchased from Sigma Chemical Co. (St Louis, Mo). Halothane was obtained from Ayerst (New York).

Human muscle biopsies

Approval by the Hahnemann University Human Studies Committee was obtained for this study. Since the diagnostic muscle biopsy for MH is not considered an investigation, no special consent other than the usual consent for surgery, was required to obtain muscle samples. Biopsies of the vastus lateralis were not selected for regions containing endplates. The pharmacological studies in tables II, III and IV were conducted on fibre bundles first exposed to halothane for the diagnostic test. Biochemical studies were conducted on tissue that could not be used for diagnostic testing because of the length or condition of the fibre bundle. Patients were selected for biopsy based on suspicion of MH, as previously described (Fletcher, Rosenberg and Hilf, 1984b). Patients were diagnosed as MH positive, MH negative or equivocal (others) based on the halothane contracture test, described below. In most cases, the muscle biopsies were obtained under femoral and lateral femoral nerve blockade; infiltration of the muscle with the anaesthetic was avoided (Berkowitz and Rosenberg, 1985).

Halothane contracture test

The muscle used in these tests was the vastus lateralis. Dimensions of the muscle strips isolated for mounting in the tissue baths were 0.5–2.5 cm (length) by 2–5 mm (width) by 1–3 mm (thickness). The preparation and stimulation of the muscle strips was essentially as described previously (Fletcher, Rosenberg and Hilf, 1984b; Fletcher and Rosenberg, 1985). Tubocurarine was omitted from the Krebs solution. Muscle strips were mounted in a 5.0-ml tissue bath containing Krebs solution at 37 °C bubbled with oxygen–carbon dioxide (95:5) and the resting tension initially adjusted to 2.0 g. The bundles were stimulated supramaximally with pulses of 2–10 ms duration at a frequency of 0.2 Hz. Following a 30-min equilibration period, 3% halothane in 95% oxygen:5% carbon dioxide was bubbled through the chamber. The halothane concentration in the gas phase was determined by gas chromatography. The time of halothane exposure was 5 min. Patients were judged MH susceptible if halothane caused contractures of greater than 0.7 g within 5 min in one out of eight strips. This was a slight departure from a previous report from our laboratory in which a response greater than 0.5 g to 1–2% halothane was considered positive (Rosenberg and Reed, 1983).

Pharmacological studies

In all cases the muscle strips used for diagnosis were equilibrated for 30 min in Krebs solution bubbled with oxygen–carbon dioxide (95:5) before use in the pharmacological studies. If a patient was clearly MH susceptible, based on the response of the first set of four strips, the studies in table I were performed on the second set of four strips. The inhibitors were added 2 min before halothane. Since the response of the second set of strips was not always identical to that of the first set, control responses (no inhibitor) were obtained in parallel with the inhibitor-treated preparations during testing of the second set of fibre bundles. Therefore, the studies in table I were always conducted on previously untreated muscle. On the other hand, for the suxamethonium and halothane interaction studies, muscle strips were first exposed to halothane for diagnostic testing and then re-equilibrated for 30 min before use in pharmacological testing. In the interaction studies, the first agent (either halothane or suxamethonium) was added to the bath 5 min before the other (suxamethonium or halothane). The two agents then remained in the bath for a second 5-min period. When inhibitors or bee venom PLA_2 were used, they were added to the bath 2 min before the initial addition of either suxamethonium or halothane. Because the response of the preparations was, on occasions, decreased by the first exposure to halothane, control responses (no inhibitor or PLA_2) were obtained in parallel with the inhibitor or PLA_2-treated preparations for each patient in these studies (tables II, III and IV). Suxamethonium was sonicated in Krebs solution and added to the 5-ml bath in a 0.5-ml volume. Spermine and indomethacin were dissolved in Krebs solution at 37 °C and the pH adjusted subsequently. For these two agents the entire bath was changed to add inhibitor. Indomethacin was not completely soluble under these conditions. Solvents such as ethanol were not used as they potentiate contractures induced by halothane (unpublished observations). Quinacrine and bee venom PLA_2 were dissolved in Krebs and injected to the bath in a 0.1-ml volume. For control preparations the appropriate amount of Krebs solution, excluding inhibitor, was added to the bath.

Spectrophotometric determination of fatty acids

Skeletal muscle was either stored in a freezer at −20 °C or used on the day of biopsy. The spectrophotometric assay of Nixon and Chan (1979) was used with slight modification. Skeletal muscle (about 0.5 g) was minced and homogenized for 30 s at 4 °C in Krebs solution 1.5 ml using a Polytron Model PT 10/35 (Brinkman) at a setting of 10. Aliquots (100 µl; about 2–4 mg of protein) of skeletal muscle homogenate were either immediately extracted with 6 ml of chloroform:*n*-heptane:methanol (4:3:2, v/v) or incubated at 37 °C for 3 h before extraction. Additional aliquots (100 µl) were removed for protein analysis. Two millilitre of sodium phosphate 100 mmol $litre^{-1}$ (pH 2.5) and 0.8 ml of H_3PO_4 100 mmol $litre^{-1}$ were then added. The aqueous methanol phase was discarded and the lower phase washed once with 1 ml of HCl 0.01 mol $litre^{-1}$. To each tube was added 2.0 ml of a copper reagent containing $Cu(NO_3)_2$ 0.1 mol $litre^{-1}$ triethanolamine 0.2 mol $litre^{-1}$, NaOH 0.06 mol $litre^{-1}$, NaCl 36%, at pH 8.1. After mixing, a 2.0-ml aliquot of the organic phase was transferred to a clean test tube. Then 0.06 ml of freshly prepared 0.4% 1,5-diphenylcarbazide in 95% ethanol containing triethanolamine 0.01 mol $litre^{-1}$ was added to each tube. Chloroform 3 ml was added and the colour was allowed to develop for 20 min at room temperature. The absorbance was read at 550 nm against a reagent blank. Palmitic acid was used as a standard. A linear standard curve was obtained between 10 and 200 nmol of free fatty acid.

Protein determination

Protein was determined by the method of Lowry and colleagues (1951), as modified by Markwell and co-workers (1978).

Data analysis

The data in tables I, II, III and IV were analysed using two-tailed paired *t* tests. The data in table V were analysed by a one-way analysis of variance followed by Duncan's multiple range test at a level of $P < 0.05$.

RESULTS

The effects of spermine, indomethacin and quinacrine were examined on halothane-induced contractures in preparations from MH positive patients. Pilot studies were conducted to determine the concentration of each PLA_2 inhibitor to be used for the studies of antagonism. Increasing the concentration of inhibitor by 10-fold increments, we sought the minimum concentration that would inhibit halothane plus suxamethonium contractures by greater than 50%. The concentration chosen for indomethacin was based on solubility considerations. A 10-fold increase of indomethacin did not appear to have any greater effect on contractures than the 1-mmol $litre^{-1}$ concentration used in these studies.

Muscle from patients diagnosed as MH susceptible is unique in that contractures can be elicited by halothane alone (table I). None of the PLA_2 inhibitors by themselves elicited significant contractures when added to the preparations at the indicated concentrations (results not shown). As is

TABLE I. *Effects of phospholipase A_2 inhibitors on (3%) halothane-induced contractures of muscle strips from MH susceptible patients. PLA_2 inhibitors were added to the bath 2 min before halothane was bubbled through the bath. The values represent the maximum contracture within 5 min of halothane addition. Values represent the mean ± SEM response for the indicated number of patients. Values significantly less than that in the absence of inhibitor:* *$P < 0.05$; **$P < 0.01$

		Response to halothane: Contracture (g)	
Inhibitor	*n*	(−Inhib.)	(+Inhib.)
Spermine 10 mmol $litre^{-1}$	6	1.40±0.35	0.19±0.10**
Indomethacin 1 mmol $litre^{-1}$	4	1.35±0.23	0.84±0.17*
Quinacrine 10 µmol $litre^{-1}$	4	1.53±0.51	0.80±0.42*

TABLE II. *Effects of phospholipase A_2 inhibitors on suxamethonium 50 mmol $litre^{-1}$-induced contractures in the presence of 3% halothane. Suxamethonium was added 5 min after halothane. Inhibitors were added to the bath 2 min before the addition of halothane. The response shown is the mean ± SEM calculated from the average of the contractures for the indicated number of patients* (n). *Significant difference when compared with absence of inhibitor:* *$P < 0.05$; ***$P < 0.001$

		Response to suxamethonium: Contracture (g)	
Inhibitor	*n*	(−Inhib.)	(+Inhib.)
Spermine 10 mmol $litre^{-1}$	4	0.80±0.21	0.05±0.03*
Indomethacin 1 mmol $litre^{-1}$	9	0.93±0.13	0.37±0.09***
Quinacrine 10 µmol $litre^{-1}$	10	0.88±0.13	0.28±0.05***

TABLE III. *Effects of phospholipase A_2 inhibitors on 3% halothane-induced contractures in the presence of suxamethonium 50 mmol $litre^{-1}$. Halothane was added 5 min after suxamethonium. Inhibitors were added to the bath 2 min before the addition of suxamethonium. The response shown is the mean ± SEM calculated from the average for the indicated number of patients* (n). *Significant difference when compared with absence of inhibitor:* **$P < 0.01$: ***$P < 0.001$

		Response to halothane: Contracture (g)	
Inhibitor	*n*	(−Inhib.)	(+Inhib.)
Spermine 10 mmol $litre^{-1}$	7	1.28±0.17	0.33±0.12***
Indomethacin 1 mmol $litre^{-1}$	9	1.26±0.20	0.83±0.16**
Quinacrine 10 µmol $litre^{-1}$	6	1.03±0.23	0.43±0.12**

shown in table I, spermine, indomethacin and quinacrine significantly antagonized halothane-induced contractures.

Muscle strips exhibiting a normal response to halothane (< 0.7 g contracture) were used in the studies presented in tables II, III and IV. Spermine, indomethacin and quinacrine also antagonized suxamethonium contractures induced in the presence of halothane (table II). In addition, the three PLA_2 inhibitors antagonized contractures induced by halothane in the presence of suxamethonium (table III).

Preparations from patients diagnosed as normal did not exhibit significant contractures to either halothane or suxamethonium when given alone (table IV). Bee venom PLA_2 alone did not cause contractures of these normal muscle strips (unpublished observations). However, pre-exposing the preparations to bee venom PLA_2 1 µmol $litre^{-1}$ resulted in significant contractures to the halothane challenge (table IV). In contrast, suxamethonium did not elicit contractures from preparations pre-exposed to PLA_2 (table IV).

Fatty acid production was stable for at least 3 weeks when nonhomogenized muscle was stored at −20 °C (unpublished observations). The free

TABLE IV. *Effects of bee venom phospholipase A_2 on 3% halothane- and suxamethonium-induced contractures of muscle strips from MH non-susceptible muscle. Bee venom PLA_2 1 µmol litre^{-1} was added to the bath 2 min before halothane or suxamethonium. The values represent the maximum contracture within 5 min of halothane or suxamethonium addition. Values represent the mean ± SEM response for six patients. **Significantly greater (P < 0.01) than that in the absence of PLA_2*

	Contracture (g)	
Agent	$-PLA_2$	$+PLA_2$
Halothane 3%	0.17±0.08	0.77±0.19**
Suxamethonium 50 mmol litre^{-1}	0.00±0.00	0.03±0.02

TABLE V. *Free fatty acid release from human skeletal muscle homogenates. Mean ± SEM (n) determinations are shown for each patient. *Significantly (P < 0.05) greater than patient 1 or 2 for the same condition*

		FFA release (nmol/mg protein)		
Patient No.	Diagnosis	Time 0	3 h	Net change
1	MH−	39±2 (4)	73±7 (3)	34±7 (3)
2	MH−	23±2 (4)	60±1 (4)	37±1 (4)
3	MH+	12±2 (4)	123±4 (4)*	111±4 (4)*
4	MH+	14±1 (4)	88±5 (4)*	74±5 (4)*

TABLE VI. *Free fatty acid release from human skeletal muscle homogenates during a 3-h incubation*

		FFA release (as % MH negatives)	
Group	*n*	Mean±SEM	Range
MH+	7	267±51	113–480

fatty acid content of unincubated muscle was not significantly greater for the two MH susceptible patients than for the two MH negative patients (table V). However, the net free fatty acid production determined at the end of the 3-h *in vitro* incubation was greater in the homogenates from the two patients susceptible to MH than from the two who were not (table V). We extended these observations to include seven MH susceptible patients. Since the absolute enzymatic activity varied from day to day, the release of fatty acid is expressed as percent of the preparation from an MH negative patient run on the same day. Muscle from six different MH negative patients were used in these studies. The fatty acid liberation for the seven MH susceptible patients was approximately 2.5 times that of the MH-negative patients (table VI).

DISCUSSION

Although the mechanisms underlying MH and halothane-induced contractures are poorly understood, there is general agreement that cytoplasmic Ca^{2+} concentrations are increased markedly under these conditions (Gronert, 1980). Could an enhanced release of unsaturated fatty acids account for the increase in myoplasmic Ca^{2+}? Exogenously administered PLA_2 can cause an increase in myoplasmic Ca^{2+} concentrations in the rat atrium as a result of release from the sarcoplasmic reticulum (Fletcher, Yang and Rosenberg, 1982). This increase in myoplasmic Ca^{2+} apparently exceeds the capacity of the cells to extrude Ca^{2+}. PLA_2 activity preferentially releases unsaturated fatty acids. A model of Ca^{2+} regulation by fatty acids has recently been proposed in which saturated fatty acids promote and unsaturated fatty acids inhibit Ca^{2+} sequestration by the sarcoplasmic reticulum (Messineo et al., 1984). In agreement with this, unsaturated free fatty acids can induce the release of Ca^{2+} from a sarcoplasmic reticulum vesicle preparation in an order of potency directly related to their degree of unsaturation (Cheah and Cheah, 1981b).

Three agents that have been demonstrated by others to inhibit PLA_2 were used in the present study. Although they are weak and non-specific inhibitors of PLA_2 activity, all three yielded similar results. Indomethacin inhibits cyclo-oxygenase at relatively low concentrations (Humes et al., 1977) and, at higher concentrations similar to that required in the present study, inhibits PLA_2 by an undefined mechanism

(Franson et al., 1980). Quinacrine (mepacrine) is a calmodulin antagonist (Volpi et al., 1981) at about the same concentration that it blocks PLA_2 activity (Walenga, Opas and Feinstein, 1981) and muscle contractures in the current investigation. Endogenous PLA_2 activity may be calmodulin-dependent (Wong and Cheung, 1979). Indeed, an increase in the concentration of calmodulin may account for the increase in PLA_2 activity observed in susceptible pigs (Cheah, 1984). Spermine inhibits PLA_2 activity at concentrations similar to that used in the present study by binding to the phospholipid bilayer and, thereby, sterically hindering the enzyme–substrate interaction (Sechi et al., 1978). The results of the present study, using three enzyme inhibitors presumedly working through different mechanisms, suggest that increases in PLA_2 activity in the skeletal muscle of MH susceptible individuals account for the greater sensitivity of these preparations to halothane. In agreement, PLA_2 activity is increased in skeletal muscle from pigs susceptible to the porcine stress syndrome (Cheah and Cheah, 1981a, b) and free fatty acid production is increased in skeletal muscle from MH susceptible patients (tables V and VI). The rate of liberation of fatty acids is very similar for susceptible pigs and MH susceptible patients. Production of free fatty acids by lipases other than PLA_2 cannot be ruled out in the human and pig studies. Although there is no evidence in the literature, it is likely that spermine, the agent used to inhibit fatty acid liberation in the study by Cheah and Cheah (1981b), inhibits lipases other than PLA_2. The increased PLA_2 activity in the pig model appears to be the result of an increase in specific activity, not concentration, of PLA_2 molecules (Cheah and Cheah, 1981b). Stress (exercise) increases blood fatty acid concentrations only in those patients diagnosed as MH susceptible (Campbell et al., 1983). This may be the result of increased serum lipase activity, suggesting a general increase in lipolysis in MH susceptible individuals.

Suxamethonium stimulates PLA_2 activity in muscle homogenates (Olthoff, Kunze and Kries, 1973) and causes normally unresponsive bundles of human muscle fibres (Fletcher and Rosenberg, 1985) and strips of rat diaphragm (Fletcher and Rosenberg, 1986) to exhibit a contracture response to a halothane challenge. Although no studies have reported that suxamethonium increases PLA_2 activity in intact tissue, pretreatment of intact preparations with bee venom PLA_2 also renders unresponsive muscle sensitive to halothane. In contrast to the results with halothane, pre-exposing preparations to bee venom PLA_2 does not result in contractures to suxamethonium. Skeletal muscle from MH positive individuals is unique in that no second agent (for example suxamethonium or bee venom PLA_2) is required for halothane-induced contractures, most likely because PLA_2 or some other lipolytic activity is increased in these patients. These results suggest that an important mechanism involved in the induction of the halothane contracture and, possibly, the MH syndrome is stimulation of lipolysis and the consequent release of unsaturated fatty acids. We speculate that halothane may increase the effects of the liberated fatty acids on Ca^{2+} regulation within the sarcoplasmic reticulum. Although the induction of the contracture by either agent requires the liberation of fatty acids, there appear to be some differences in the mechanisms of contracture induction by halothane and suxamethonium (Fletcher and Rosenberg, 1986). At this time we cannot eliminate the possibility that PLA_2 activation may be the result of a greater influx of Ca^{2+} in MH muscle, as PLA_2 is a Ca^{2+}-dependent enzyme.

One difference that has been observed between human skeletal muscle and rat diaphragm preparations is the effect of quinacrine on halothane-and suxamethonium-induced contractures. Although quinacrine antagonizes halothane- (tables I and III) and suxamethonium-induced (table II) contractures in human preparations, quinacrine enhances halothane- and suxamethonium-induced contractures in the rat diaphragm (Fletcher and Rosenberg, 1986). The reason for this difference is unknown, but may relate to slightly dissimilar quinacrine binding characteristics of the PLA_2 enzyme from human as compared with that from the rat. Other possibilities are discussed in the accompanying paper (Fletcher and Rosenberg, 1986). Whatever the reason for this discrepancy, the use of these two model systems in comparative studies may help elucidate the role of lipolysis in contracture induction.

Therefore, there appears to be a role for enhanced lipase activity in contracture induction by halothane and in human MH. In addition, the interaction between suxamethonium and halothane observed *in vitro* appears to be dependent on stimulation of PLA_2 activity by suxamethonium.

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DISTRIBUTION OF TRICHLOROETHYLENE BETWEEN PLASMA AND ERYTHROCYTES IN WHOLE BLOOD FROM FASTING SUBJECTS

D. D. DAVIES, R. B. DOUGLAS AND S. LING

SUMMARY

The plasma:erythrocyte distribution ratio of trichloroethylene at room temperature was determined by a direct method using 10 separate blood samples. The trichloroethylene content of plasma was lower than that of the erythrocytes by a ratio having a mean value of 0.63 (SD 0.05, range 0.56–0.74).

In 1947, Powell found that the Ostwald solubility coefficient of trichloroethylene, at 20 °C, was greater in whole blood than in plasma. Soucek (1955) carried out similar determinations at 37 °C and also found that the solubility coefficient of the agent was greater in whole blood than in plasma. These findings would suggest that the plasma: erythrocyte distribution ratio of trichloroethylene is less than unity at both 20 °C and 37 °C.

It was decided to determine the plasma: erythrocyte distribution ratio of trichloroethylene by a direct method, as knowledge of such a ratio was considered to be of some importance when reviewing the distribution pharmacokinetics of the agent. For technical reasons the determinations were all carried out at room temperature (20–22 °C).

MATERIALS AND METHODS

A blood sample (10 ml) obtained from each of 10 fasting patients who were undergoing trichloroethylene anaesthesia, was taken into a heparinized syringe. Five millilitre of each sample was transferred to a 5-ml disposable syringe of polystyrene and silicone rubber. The syringe was sealed with a plastic cap and kept for at least 20 h. During the last 1 h the syringe was rotated on a mechanical rotator. The remainder of each blood sample was used for the determination of the haematocrit.

Immediately following rotation of the syringe, a 200-µl aliquot of blood was taken and injected to 5 ml of n-heptane contained in a measuring flask and the whole shaken for 2 min. The 200-µl aliquot was obtained by, first, removing the plastic cap sealing the syringe and replacing it with a thin rubber cap (Micro tube closures M-375 (Scientific Ind. Inc.)), piercing the latter cap with the needle of a microsyringe, then pushing blood through the microsyringe in a retrograde manner to obviate errors attributable to deadspace (Davies, 1978).

The 5-ml disposable syringe containing the rest of the blood was re-sealed firmly with a plastic cap and spun at 2000 rev min^{-1} for 20 min in a centrifuge. The syringe was placed in the centrifuge in such a way that the cells "gravitated" towards the plunger end of the syringe. After centrifuging, the syringe was held vertically with the plunger end downwards. Two 100-µl aliquots of plasma and of red cells, respectively, were measured using a technique similar to that described for blood and these samples were injected to 5 ml of heptane.

The trichloroethylene contents of the n-heptane that had been equilibrated, respectively, with blood, with plasma and with cells, were determined using a gas chromatograph with electron-capture detection (Davies, 1978).

When the trichloroethylene contents of whole

D. D. DAVIES, PH.D., F.F.A.R.C.S., Research Department of Anaesthetics, Royal College of Surgeons of England, London WC2. R. B. DOUGLAS, PH.D., M.SC., London School of Hygiene and Tropical Medicine, London WC1E 7HT. S. LING, M.B., CH.B., F.F.A.R.C.S., St Helier Hospital, Wrythe Lane, Carshalton, Surrey SM5 1AA.

TABLE I. *Trichloroethylene content in plasma, erythrocytes and whole blood samples from 10 patients, together with the ratios of distribution. Determinations were carried out at temperatures ranging from 20 to 22 °C*

		Trichloroethylene content (mg dl^{-1})					
Subject	Haematocrit (%)	Whole blood	Plasma	Erythrocytes	Calculated whole blood	Difference between calculated and actual blood content (%)	Plasma: erythrocyte content ratio
1	47	6.58	4.77	8.60	6.57	−0.2	0.56
2	44	4.18	3.13	5.17	4.03	−3.6	0.61
3	46	3.90	3.00	4.70	3.78	−3.1	0.64
4	43	2.46	1.88	3.08	2.40	−2.4	0.61
5	42	3.76	3.16	4.27	3.63	−3.5	0.74
6	50	5.24	4.10	6.40	5.25	+0.2	0.64
7	46	8.12	6.56	9.60	7.94	−2.3	0.68
8	50	6.10	4.76	7.72	6.26	+2.7	0.62
9	54	5.72	4.17	7.05	5.71	−0.2	0.59
10	47	6.55	5.00	7.75	6.30	−3.8	0.65

blood, plasma and packed cells had been obtained, the plasma:erythrocyte distribution ratios were determined for each of the blood samples. The trichloroethylene contents of whole blood were obtained independently by calculation knowing the plasma and the erythrocyte contents, and the haematocrit. These values were compared with the directly measured values.

All the analyses were carried out at room temperature; this varied from 20 to 22 °C.

(It had been found that the trichloroethylene content of blood samples stored in the 5-ml disposable polystyrene syringes decreased slightly during storage, but that after 20 h of such storage there was, subsequently, no measurable change in the trichloroethylene content during an approximate 30-min period of time—the time interval that was required for centrifuging and sampling.)

RESULTS

With determinations conducted at temperatures between 20 and 22 °C, the trichloroethylene content of plasma was lower than that of the erythrocytes by a ratio having a mean value of 0.63 (SD 0.05; range 0.56–0.74; $n = 10$) (table I). The trichloroethylene content of the blood samples used ranged from 2.46 mg dl^{-1} to 8.12 mg dl^{-1}. The calculated values for the trichloroethylene content of whole blood derived from plasma and erythrocyte contents and the haematocrit, differed from the measured values by a mean factor of 2.2%. The maximum difference was 3.8%.

DISCUSSION

The fact that the plasma: erythrocyte content ratio of an agent diverges from unity will mean that, at a constant partial pressure of the agent, its content in the blood may alter with changes in the cell volume of the blood. In the case of trichloroethylene, with a plasma:erythrocyte distribution ratio of 0.63, a reduction in the cell volume of the blood would be expected to reduce, significantly, the blood solubility of the agent and hence its blood content at a set partial pressure.

It is possible that the value of the distribution ratio at body temperature could differ slightly from the value of the ratio at ambient temperature. For the determination of the distribution ratio at 37 °C it would have been necessary to use a temperature controlled centrifuge and sampling chamber. These latter were not available and, therefore, only the ratio occurring at ambient temperature could be obtained. It was not possible, by theoretical calculation, to ascertain the exact difference between these two ratios.

The reason for the preferential solubility of trichloroethylene in the red cells is not fully understood. Three factors could affect the distribution of the agent: water solubility, lipid solubility and protein affinity.

Water solubility would have the effect of concentrating the agent preferentially in the plasma as the water content of the plasma exceeds the water content of the erythrocytes: Grüner (1957) found a plasma:erythrocyte water content ratio of 1.53; Prankerd (1961) gave a ratio of 1.35.

The effect of water solubility in determining blood distribution of an agent will, however, be of significance only if the agent is one having marked water solubility. In the case of trichloroethylene such effect should, therefore, be slight.

With regard to lipid solubility, any difference in its concentration between the plasma and the erythrocytes should have a marked effect on the distribution of trichloroethylene as the agent has a high lipid solubility. There does appear to be, in adult fasting subjects, a somewhat higher concentration of lipid in the plasma than in the erythrocyte: various estimates of the total lipid content of the erythrocyte have given values between 4.08 and 6.12 g litre^{-1} and estimates of the total lipid content of the plasma have given values between 7.03 and 8.12 g litre^{-1} (*Documenta Geigy*). The effect of lipid solubility on the distribution of trichloroethylene would thus seem to favour preferential concentration of the agent in the plasma.

However, protein affinity would appear to play a dominant and overriding role in concentrating trichloroethylene preferentially in the erythrocyte as the protein content of the erythrocyte exceeds the protein content of the plasma by a factor of nearly 5, and trichloroethylene has been shown (Powell, 1947) to have a marked affinity for haemoglobin. However, the net effect of protein affinity may not be simple or clear cut as plasma protein affinity for trichloroethylene probably also exists and this may exert a moderating influence on the concentrating effect of the haemoglobin.

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A CONSTANT CURRENT PERIPHERAL NERVE STIMULATOR (NEUROSTIM T4)

Description, and Evaluation in Volunteers

T. POLLMAECHER, H. STEIERT AND W. BUZELLO

SUMMARY

A pocket-size, battery-powered peripheral nerve stimulator featuring a calibrated constant current floating output (max. 80 mA) was evaluated in unanaesthetized volunteers. Modes of stimulation included continuous 1 Hz, continuous train-of-four every 15 s, and on-demand tetanus (50 Hz per 5 s). Within the limits of 0–250 V, voltage adjusted automatically for 0.2-ms monophasic square pulses. Between 20 and 80 mA, the dial error of current intensity was less than ±5%. Maximum allowable resistance for the generation of 40-mA pulses was 5 kΩ—that is five times the average tissue impedance as measured in 15 volunteers. With surface electrodes, the current intensity required for maximal indirect muscle stimulation in another 50 individuals was 38±23 mA (mean±SD). With up to 80 mA stimulus current, supramaximal nerve stimulation was obtained in 94% of the volunteers.

When comparing six commercially available nerve stimulators, Mylrea and colleagues (1984) found that current output was inconsistent in all models and considered a constant current nerve stimulator highly desirable. The present device (Neurostim 4) was designed by the authors to generate constant current stimuli with defined current intensity and, as such, differs from a comparable instrument which delivers constant, but not calibrated, pulses (Viby-Mogensen et al., 1980). (Neurostim 4 is manufactured by Hugo Sachs Elektronik KG, P.O. Box 9, D 7801 March, Federal Republic of Germany; Linton Instrumentation, Hysol Harlow, Essex CM18 6QZ, United Kingdom; Resuscitation Laboratories, P.O. Box 2351, Bridgeport, CT 06608, U.S.A.)

TECHNICAL DESCRIPTION

The Neurostim T4 (figs 1, 2; table I) is a pocket sized, battery-powered, calibrated constant current nerve stimulator which may be used either with integrated or with cable electrodes. Within the limits of 0–250 V, the voltage adjusts automatically for 0.2-ms monophasic square pulses dialled in mA. Stimulus features are *continuous 1-Hz*, *continuous train-of-four* (T4; 2 Hz every 15 s) and 50 Hz *tetanic*. A *continuous/standby* switch allows the operator to discontinue ongoing stimulation without altering the setting of the dial. If, in T4 mode, the selector switch is reset from *standby* to *continuous*, T4 stimulation will be resumed without delay. A 5-s train of 50 Hz is elicited manually either without delay by depressing the *tetanus* key in *standby* mode, or after a delay of 10 s when the tetanus key is depressed in *continuous* mode. The interval between the last tetanic and the first post-tetanic stimulus is 1 s with *single* and 15 s with *T4* stimulation. A floating current output prevents the nerve stimulator from being triggered by high-frequency current or electrical leakage from surrounding equipment. Three light emitting diodes (LED) monitor battery power, electrode connection and tetanus delay.

Thomas Pollmaecher,* M.D.; Walter Buzello,† M.D.; Department of Anaesthesiology, University Hospital, Hugstetter Str. 55, D 7800 Freiburg, Federal Republic of Germany. Hermann Steiert, Electronics Engineer, Hugo Sachs Elektronik KG, D 7806 March, Federal Republic of Germany.
Present addresses:
* Max-Planck-Institut für Psychiatrie, Kraepelinstr. 2 und 10, D 8000 Muenchen 40, W. Germany.
† Department of Anaesthesiology, University Hospital, Joseph-Stelzmann-Str. 9, D 5000 Köln 41, Federal Republic of Germany.

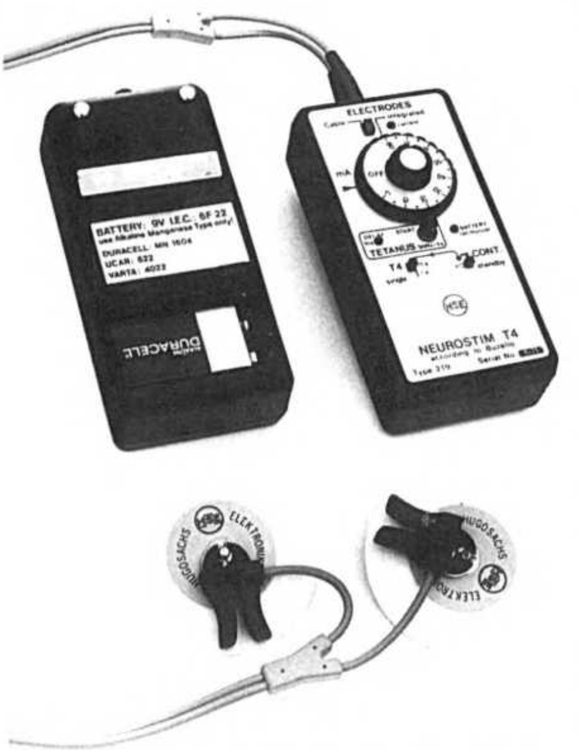

FIG. 1. Neurostim T4 peripheral nerve stimulator.

PERFORMANCE TESTING

Subjects, materials and methods

The electricial performance of the nerve stimulator was evaluated as described by Mylrea and colleagues (1984). With 20-, 40- and 80-mA dial settings, the current wave form was displayed on a storage oscilloscope, and the actual stimulus intensity was recorded as a function of voltage into fixed non-inductive resistances between 0.1 and 100 kΩ. The accuracy of the dial setting was measured in eight instruments for 10, 20, 40, 60, and 80 mA into a 1-kΩ load. Battery life (Duracell MN 1604) was determined with four instruments in *continuous T4* mode with 40 mA into a 500-Ω load.

TABLE I. *Technical data of the Neurostim T4 peripheral nerve stimulator. *Meeting standards of IEC 601 (International Electrotechnical Commission)*

Type of output	Constant current, fully isolated, BF type*
Current intensity	0–80 mA
Maximum voltage	250 V
Pulse width	0.2 ms
Stimulation features	Single (1 Hz) Train-of-four (2 Hz/2s) every 15 s Tetanic (50 Hz/5s); manual
Electrodes	Cable: surface, needles Integrated: surface
Power supply	9-V block battery (alkaline—manganese)
Size	60 × 120 × 50 mm
Weight	250 g

The stimulus intensity for maximal nerve stimulation was measured in 50 conscious volunteers. The ulnar nerve was stimulated at the wrist with 1 Hz and T4, using silver–silver chloride surface electrodes placed 5 cm apart, without pretreatment of the skin. Twitch tension of the adductor pollicis muscle was recorded by means of a boomerang force displacement transducer (Walts, 1973), providing a 150–200 g resting

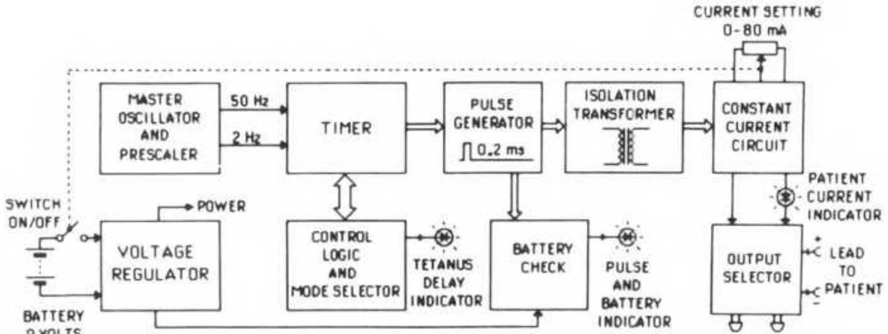

FIG. 2. Schematic diagram of the Neurostim T4 peripheral nerve stimulator.

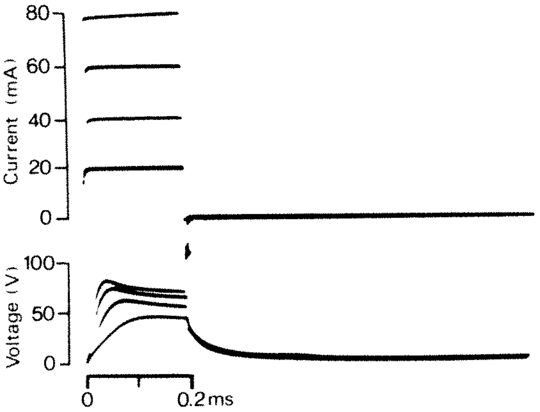

FIG. 3. Square wave current output of the Neurostim T4 peripheral nerve stimulator. Upper traces: current output. Bottom traces: voltage between electrodes automatically adjusting for square wave current output. Voltage and mA curves are corresponding in their order from bottom to top.

thumb tension. The recording system was allowed to stabilize during a 10-min period of indirect muscle stimulation with 20 mA. The current intensity was then reset to zero and afterwards increased in 5-mA increments every sixth *single* or every fourth *T4* stimulus, respectively. A current intensity response curve was constructed and the intensity for minimum, 90% and maximum twitch response was obtained from the curve. Skin resistance was measured in another 15 volunteers for 30-, 60- and 80-mA stimulus intensity. For this purpose, a 100-Ω resistor was connected serially in the stimulation circuit, and the voltage was measured at the skin electrodes as a function of current intensity. All results were calculated as means, standard deviations and ranges. Statistical significance was assessed by paired Student's *t* test.

TABLE II. *Stimulus intensity required for different levels of indirect muscle stimulation in* train-of-four (*T4*) *and* single (*1 Hz*) *mode: minimum twitch response* (I_{min}), *maximum twitch response* (I_{max}) *and 90% twitch response* (I_{90}). *Figures represent mA* (*mean ± SD and range*). *At* P = *0.05, there is no significant difference between T4 and 1 Hz stimulation*

Stimulus	I_{min} ($n = 50$)	I_{max} ($n = 47$)	I_{90} ($n = 50$)
T4 (mA)	17 ± 5 (10–40)	33 ± 17 (15–75)	25 ± 11 (13–47)
1 Hz (mA)	16 ± 6 (10–35)	38 ± 23 (15–70)	27 ± 12 (14–48)

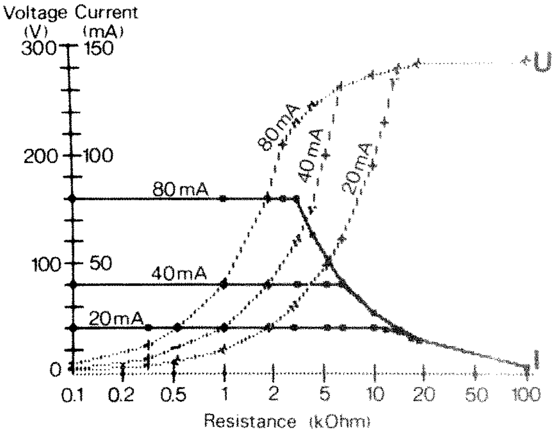

FIG. 4. Voltage (dotted lines) delivered by the Neurostim T4 peripheral nerve stimulator for constant current output (solid lines) as a function of resistance.

Results

The nerve stimulator delivered 0.2-ms square pulses with adequate accuracy and reproducibility (fig. 3, upper panel). Maximum twitch response was obtained in 94% of the 50 volunteers (age 25 ± 5 yr; body weight 72 ± 10 kg). In three individuals, however, it could not be clearly defined (table II). No significant differences existed between 1 Hz and T4 stimulation in eliciting minimum, 90% and maximum twitch responses (table II). Skin resistance, in 15 conscious volunteers (age 37 ± 12 yr; body weight 69 ± 10 kg), was 1.9 ± 0.5 (1.3–2.6) kΩ with 30 mA, 1.2 ± 0.3 (0.8–2.0) kΩ with 60 mA and 1.0 ± 0.2 (0.7–1.3) kΩ with 80 mA. The dial error of current intensity was less than ± 5% (table III). The 250-V maximum voltage was sufficient to maintain constant current stimuli as long as the load impedance was less than 5 kΩ for 40 mA; that is, less than five times the average skin resistance. Figure 4 gives details of the constant current output as a function of resistance and voltage:

TABLE III. *Accuracy of dial setting, measured into a 1-kΩ impedance with eight different Neurostim T4 nerve stimulators. Means ± SD and ranges*

mA dialled	10	20	40	60	80
mA measured	9.3 ± 1 (8–11)	19.8 ± 1 (18–21)	39.9 ± 1.7 (38–42)	61.4 ± 1.4 (60–64)	79.9 ± 0.8 (78–81)

with supramaximal nerve stimulation and a dial setting of, for example, 20 mA, the maximum allowable impedance is 10 kΩ (fig. 4, bottom solid line). The voltage resulting from the same dial setting is 8 V into 0.5 kΩ, 20 V into 1 kΩ, 100 V into 5 kΩ, and 250 V into 10 kΩ (fig. 4, right dotted line). Corresponding figures may be read from the 40- and 80-mA lines. Battery life was more than 2000 h.

DISCUSSION

It has been emphasized that current rather than voltage determines neural stimulation (Mylrea et al., 1984). Consequently, nerve stimulators should be designed to generate pulses of calibrated current rather than voltage. The Neurostim T4 is characterized by satisfactory performance with respect to both intensity of stimulus and wave form.

Although recommended for use in anaesthetized patients, the instrument was tested in conscious volunteers in order to preclude any possibility that anaesthesia might interfere with neuromuscular transmission. In terms of maximum current and voltage, the limits of performance of the nerve stimulator compare favourably with the physiological ranges of tissue impedance and intensity of stimulation required for maximum twitch response. However, there was a 6% failure rate among the volunteers in whom supramaximal nerve stimulation could not be obtained with surface electrodes, even with 80 mA.

Because of the physiological strength–duration relationship, the current intensity for indirect muscle stimulation decreases with increasing pulse width. However, the pulse width must be clearly less than 0.3 ms, to avoid repetitive nerve firing (Epstein et al., 1969). The safety standards of the International Electrotechnical Commission (IEC) prohibit current intensities of more than 80 mA to be administered to humans. Within these limits, the 0.2-mA pulses and 80-mA maximum current represent the best acceptable combination. Needle electrodes may be used should supramaximal nerve stimulation not be obtained from the maximum available stimulus current. It has to be realized, however, that with needle electrodes a much smaller current intensity has to be applied than with surface electrodes.

The selection of stimulus patterns was restricted to those relevant to clinical anaesthesia. The trains-of-four were separated by as much as 15 s so as to overcome reliably any residual slow fade which, potentially, may be effective for as long as 10 s after the preceding stimulus (Lee, 1975). Since the response of the first stimulus of each train-of-four is identical to the response to *single* stimulation every 10–15 s, a separate low frequency *single* stimulus mode, such as 0.1 Hz, was not incorporated.

Preferentially, the 1-Hz mode may be used for rapid identification of the best site for nerve stimulation and for adjustment of supramaximal stimulation in the absence of neuromuscular blockers. The integrated electrodes, adopted from Churchill-Davidson's nerve stimulator (1965), are convenient for short-term use such as in the differential diagnosis of peripheral *v.* central respiratory depression.

From the user's point of view, it would appear desirable to have the integrated electrodes disconnected automatically upon attachment of the cables, rather than having to operate a selector switch. At the present state of development, the housing leaves no room for the appropriate logic. However, future series may be redesigned for this modification as well as for a fourth LED, which would monitor the actual intensity of current relative to the mA dialled.

In conclusion, this is a new battery-powered nerve stimulator for routine use in clinical anaesthesia with calibrated constant current output. Its handy size and extremely low energy consumption are other attractive features. The performance characteristics of the apparatus provide the accuracy and the reproducibility of a research grade instrument.

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ASSESSMENT OF THE DATEX RELAXOGRAPH DURING ANAESTHESIA AND ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE

J. A. CARTER, R. ARNOLD, P. M. YATE AND P. J. FLYNN

Accurate assessment of neuromuscular function requires the stimulation of a motor nerve and the recording of the evoked mechanical or electromyographic response (EMG). Measurement of the evoked tension in muscle involves problems with transducer fixation and overload, and immobilization of the arm (Ali and Savarese, 1976). In general, these systems are cumbersome and difficult to set up in clinical practice. The advantages of measuring the EMG are that a response may be obtained from muscles which are not accessible for mechanical recording and it may be used in paediatric patients. Traditionally, the recording of the EMG required the use of a preamplifier and storage oscilloscope and, as a result, its use was restricted. With modern microprocessor technology it is now possible to detect, analyse, digitize and record the EMG without the need for a storage oscilloscope.

The Datex Relaxograph is a neuromuscular transmission analyser which utilizes the integration of the EMG response. It is a modified form of the neuromuscular transmission monitor (NTM) of the Datex Anaesthesia Brain Monitor (ABM) and is now marketed as a separate unit (fig. 1). We have been using this machine and have compared its results with those provided simultaneously with a force transducer.

SUMMARY

The Datex Relaxograph is a recently introduced electromyographic monitor of neuromuscular transmission. It has been assessed in patients requiring neuromuscular blockade and the results compared with those obtained simultaneously with a force transducer. There was a good correlation between the two methods of measurement for both twitch height and train-of-four ratio (correlation coefficients 0.93 and 0.97, respectively). The Datex Relaxograph proved easy to use in the clinical setting.

MATERIALS AND METHODS

Apparatus

The Datex Relaxograph uses small disposable pre-gelled silver–silver chloride surface electrodes for nerve stimulation and EMG recording. The two stimulating electrodes may be positioned over the median, ulnar or posterior tibial nerves. As a result of the differential amplification utilized by the monitor, only one recording electrode is required on the appropriate muscle, ideally over the motor point of the muscle stimulated. When the active electrode is placed over the thenar or hypothenar eminence, it may be advantageous to place the indifferent electrode at the tip of the first or fifth finger, respectively, although it can be positioned elsewhere on the hand if the patient is small or large ECG electrodes are used. In order to decrease stimulus artefact, the fifth electrode (ground electrode) is positioned between the stimulating and the recording electrodes and the EMG response is gated; that is, the electronic integration lasts for 10 ms, starting 3 ms after the

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John A. Carter, M.A., F.F.A.R.C.S., Paul M. Yate, M.B., B.S., F.F.A.R.C.S., Patricia J. Flynn, M.B., B.S., F.F.A.R.C.S.I. (Anaesthetics Unit); Richard Arnold, M.B., B.S., F.F.A.R.C.S. (Department of Anaesthetics); London Hospital Medical College, Whitechapel, London E1 1BB.
Correspondence to P.J.F.

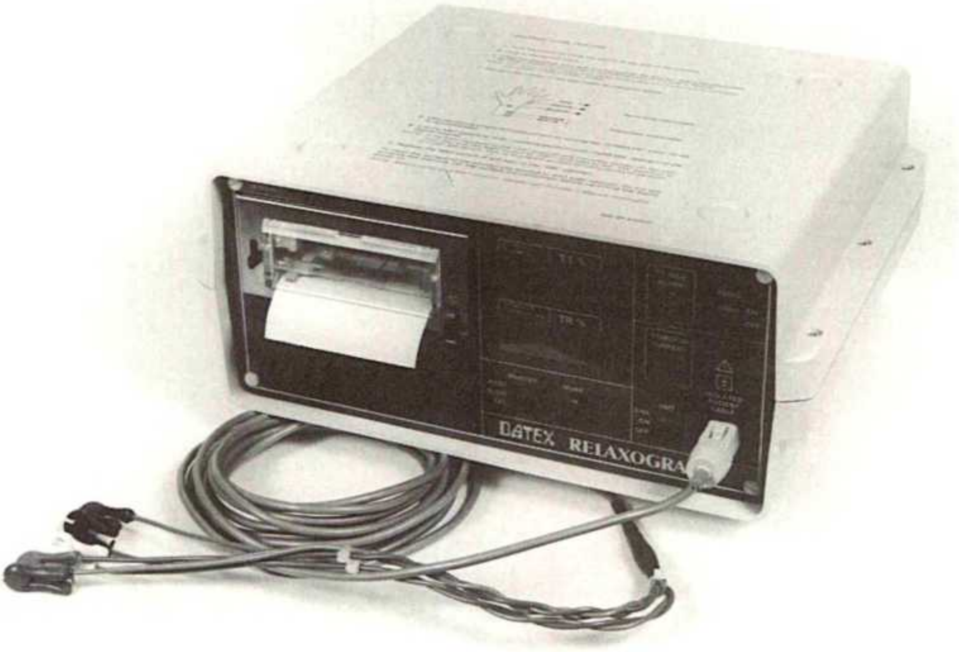

FIG. 1. The Datex Relaxograph.

nerve is stimulated. The signal detected by the analyser is processed by an amplifier, a rectifier and an electronic integrator. The results are displayed, sampled and held for a variable period in the memory of the computer. The machine uses a fully isolated constant current stimulator which produces train-of-four (TOF) stimuli, with a pulse width of 100 μs and a frequency of 2 Hz every 20 s. The stimulus output is a rectangular wave with a current range of 0–70 mA and the machine calibrates automatically by searching for the optimum signal levels before setting the supramaximal level. The calibration sequence usually takes less than 20 s. As it is both potentially painful and easily affected by patient movement, it must be initiated after the patient is anaesthetized, but before neuromuscular transmission is blocked. After locating the supramaximal stimulus for the patient (to set the 100% reference values) the time-elapsed clock is reset automatically and starts counting.

Every 20 s the monitor calculates the percentage of first twitch amplitude compared with the reference (T1), and the train-of-four (TOF) ratio (the ratio of last twitch height to first height). These values are shown on two digital displays. When less than four responses are elicited, the TOF ratio is replaced by a number of dots, representing the responses that can be recorded. The machine also incorporates a silent hard-copy printer which includes the results of the automatic calibration procedure and error messages. The printer has two speeds: one for recording every response of the train-of-four and the other for maximally compressed trend recording, giving only the first and fourth responses.

If neuromuscular blocking drugs have been given to the patient before calibration, the instrument can be used in an uncalibrated mode and will measure TOF ratios.

There is also backup power for the calibration memory so that the machine can be unplugged from its power supply for up to 15 min without the need to recalibrate.

Patients and anaesthesia

Twenty patients were studied: all required surgical relaxation for a variety of procedures. None had existing neuromuscular disorders. All were premedicated with either temazepam 10–20 mg by mouth or papaveretum 10–20 mg and hyoscine 0.2–0.4 mg i.m.

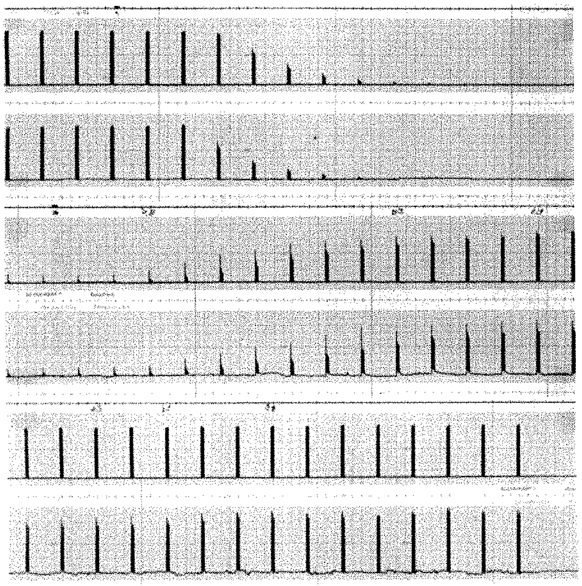

FIG. 2. Recordings of onset and recovery of neuromuscular blockade monitored by the Relaxograph (upper traces) and force transducer (lower traces).

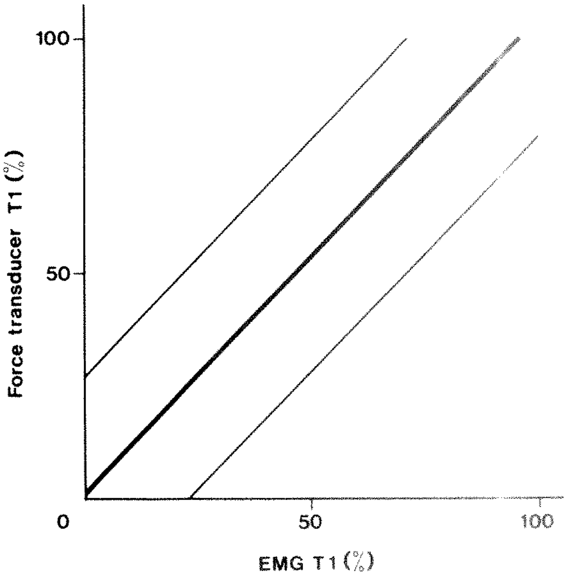

FIG. 3. Results from 1078 measurements of first twitch (T1) from the force transducer and the Datex Relaxograph. The best fitted straight line was calculated by least squares regression. The 95% tolerance limits are also shown. $Y = 1.05 + 1.03X$; $r^2 = 87\%$.

The five electrodes of the Datex Relaxograph were attached after cleaning the skin thoroughly with alcohol. The stimulating electrodes were applied over the ulnar nerve and the recording electrodes over the thenar eminence. The ground electrode was placed between the stimulating and recording electrodes. A force transducer (Gould–Statham UC3) was then attached to the thumb of the same hand and strapped into position. The arm was fixed in a splint. The output from the Relaxograph was recorded on one channel of a pen recorder (Gould 220) and the amplified signal from the force tranducer was displayed on the second channel. Thus, the electromyographic and mechanical responses to the same stimulus could be compared simultaneously (fig. 2).

Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and maintained with 67% nitrous oxide in oxygen and increments of fentanyl 0.1–0.2 mg. Evoked mechanical and electromyographic responses were allowed to stabilize and control values were obtained before the administration of atracurium 0.5 mg kg^{-1}. Supplements of atracurium 0.1–0.3 mg kg^{-1} were given as required. Halothane 0.5–1% was added to the inspired gases in some cases. Neuromuscular blockade was antagonized in all patients with neostigmine 2.5 mg (plus atropine 1.2 mg).

A further five patients were studied to assess the degree of stability of the Datex Relaxograph. All were young and fit and required intubation of the trachea for routine dental surgery. The Relaxograph was attached in the same manner as before, but without the addition of the force transducer. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and maintained with 67% nitrous oxide in oxygen plus 1–2% halothane. After calibration of the Relaxograph, the value of the supramaximal stimulus was noted and suxamethonium 1 mg kg^{-1} was administered to facilitate tracheal intubation. At the end of the procedures (operating time 25–90 min) the instrument was recalibrated and the second supramaximal stimulus noted.

RESULTS

An example of the recordings obtained simultaneously from both the Relaxograph and the force transducer is given in figure 2, showing the onset and recovery of neuromuscular blockade. The results of 1078 consecutive measurements of first twitch (T1) from the Relaxograph and from the force transducer are shown in figure 3. The best fitted straight line was calculated by the method of least squares regression. The correlation coeffici-

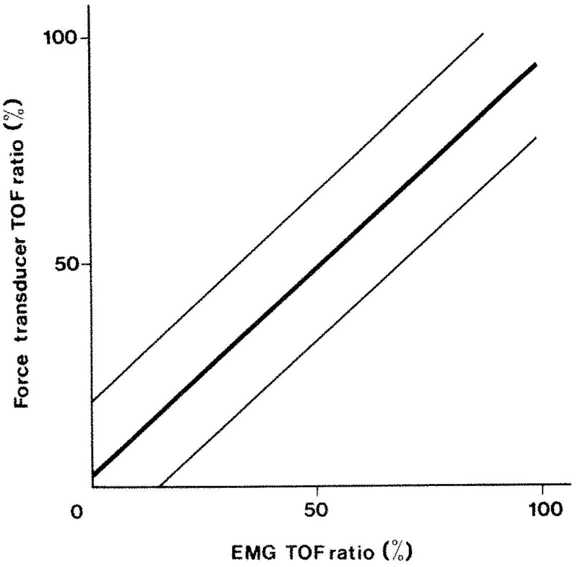

FIG. 4. Results from 683 measurements of train-of-four (TOF) ratio. The regression line and 95% tolerance limits are shown. $Y = 1.69+0.914X$; $r^2 = 93.7\%$.

ent was 0.933. Figure 4 shows the results from 683 simultaneous recordings of TOF ratio. The correlation coefficient was 0.968. Ninety-five percent tolerance limits are shown for the results on both graphs. For TOF ratio, the Relaxograph tended to underestimate the degree of blockade as compared with the force transducer. This was most marked when neuromuscular transmission was least impaired.

The additional five patients, who received suxamethonium, had all regained full neuromuscular function after 30 min (as seen by TOF ratio returning to 100%). In all five, the supramaximal stimulus remained the same after recalibration.

DISCUSSION

There are many persuasive arguments for trying to measure the degree of neuromuscular blockade produced by neuromuscular blockers. The variation in individual response to these drugs is considerable. Katz (1967) found that, following the administration of tubocurarine 0.1 mg kg^{-1}, twitch height was unaffected in 6% of patients while 7% showed 100% twitch depression. Similar results have been described with other myoneural blockers (Norman, 1982). Another advantage is that the need for incremental doses can be easily noted by the anaesthetist. Monitoring of neuromuscular blockade will also allow the anaesthetist to determine whether the administration of anticholinesterases is necessary, and to predict the circumstances where they are likely to produce a rapid or slow antagonism of blockade.

Many methods have been suggested to quantify the degree of neuromuscular blockade (Ali and Savarese, 1976). More than 25 years ago, Churchill-Davison and Christie (1959) proposed that nerve stimulators be used. The only satisfactory way to monitor neuromuscular function is by stimulation of an accessible peripheral motor nerve and the measurement of the evoked response in the skeletal muscle innervated by that nerve. Since the adductor pollicis brevis is the only muscle producing adduction of the thumb which is supplied by the ulnar nerve (Merton, 1954), this ulnar adductor method most closely resembles an experimental nerve–muscle preparation (Ali, 1985) and is most often used.

EMG recording has several advantages over the measurement of tension (Epstein and Epstein, 1973; Lee et al., 1977; Lam, Cass and Ng, 1981). Once the electronic systems were developed, machines that record and process the evoked EMG could be made compact and easy to use. This development was foreseen more than 20 years ago (Katz, 1965). The problems in the use of a force transducer can be avoided: the need for absolute immobility with adequate fixation, and overload and preload adjustment on certain systems (Epstein and Epstein, 1973). The EMG monitor is not affected by changes in muscle contractility and has a more rapid response (Viby-Mogensen, Jorgensen and Ording, 1979). The criticisim that systems for assessing the degree of neuromuscular blockade are too clumsy and difficult to use in clinical practice may no longer be applicable to the newer generation of electromyographic monitors (Lam, Cass and Ng, 1981).

The Datex Relaxograph is compact and of modular design. It fits comfortably on a standard British anaesthetic machine. Only five electrodes have to be placed on the patient's arm. We found that paediatric ECG electrodes were adequate in most patients, although they were often trimmed. For longer procedures the greater adhesiveness of the Datex electrodes was preferable. In obese patients the position of the stimulating electrodes was critical if the machine was to find the supramaximal stimulus current. If these had to be repositioned, the time in the anaesthetic room was increased and, as the repositioning had to be done after induction of anaesthesia, such adjustment was inconvenient.

There are also potential disadvantages involved in the use of EMG monitors. Stability may be a problem in some cases, the exact cause of which remains unclear. Fixation of the hand may still be desirable with these machines as changes in the relative positions of recording and stimulating electrodes may alter the measured evoked response. The effect of other drugs, in addition to the neuromuscular blockers, has never been investigated thoroughly and the effects of changes in pH, blood-gas tensions and electrolyte concentrations remain to be defined. The greatest effect, however, may be caused by changes in electrode impedance which increase with time and with changes in temperature. In five control patients, the supramaximal stimulus value remained stable after recovery from suxamethonium. It should be noted, however, that these procedures were of short duration (less than 90 min) and were not associated with the opening of body cavities with subsequent major heat loss or poor peripheral perfusion.

We found the Datex Relaxograph gave a reliable assessment of neuromuscular function. Correlation with a well-proven mechanical system was good. Others have studied the relationship between EMG analysers and force transducers, with varying results (Ali, Utting and Gray, 1971; Lee et al., 1977; Lam, Cass and Ng, 1981). Shanks and Jarvis (1980) stated that, while the adductor pollicis muscle and the adjacent interosseous muscles are supplied by the ulnar nerve and while the mechanical twitch measurement of thumb adduction approaches the single nerve–muscle preparation, the compound EMG obtained from surface electrodes can never be as precise. They concluded, however, that evoked EMG measurements would appear to provide a more reliable index of blockade than the mechanical twitch response. Their data suggested that either EMG amplitude or the rectified, integrated signal would be equally suitable in the assessment of neuromuscular blockade. It is likely that the relationship between electromyographic and mechanical responses varies for different neuromuscular blockers and we chose to use only atracurium in an effort to avoid this potential error. The relationship has also been shown to vary according to which muscle or muscle group is stimulated (Katz, 1973). Drugs which affect muscle contractility may alter the results obtained from the force transducer (Lee and Katz, 1980) so the relationship may be disturbed by the use of volatile agents (Foldes et al., 1983). The effect of halothane was found to be insignificant in our study.

Previous workers (Epstein and Epstein, 1973; Katz, 1973; Windsor, Sebel and Flynn, 1985) have found that assessing neuromuscular function electromyographically leads to underestimation of the degree of blockade, especially at lower levels of neuromuscular transmission. Windsor and colleagues (1985) found this underestimation was slightly more pronounced when comparing TOF ratios. We also found this result when comparing TOF ratios, but not when comparing the twitch response.

In conclusion, we have assessed the Datex Relaxograph in clinical use. It produces accurate and coherent information about the state of muscle relaxation and it is convenient to operate.

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PHAEOCHROMOCYTOMA

Diagnosis, Preoperative Preparation and Anaesthetic Management

C. J. HULL

SUMMARY

Unless patients harbouring this uncommon tumour are correctly prepared and protected from the effects of excessive catecholamine release, they are greatly at risk when undergoing surgical procedures of any kind. This short review describes the clinical syndromes associated with phaeochromocytoma, the diagnostic procedures which may identify and localize the tumour(s), the principles and practical aspects of pharmacological control, and a method of anaesthetic management which has proved safe and effective in many patients.

Phaeochromocytoma is a rare tumour which secretes catecholamines, often in massive quantities. Encounters with phaeochromocytoma may occur when anaesthetizing suspected cases for invasive radiological procedures, anaesthetizing proven cases for surgical removal or, most dangerous of all, when anaesthetizing unsuspected cases for surgical procedures (Darby and Prys-Roberts, 1976; Wooster and Mitchell, 1981; Bittar, 1982; Jones and Durning, 1985). In addition, patients may be admitted to the Intensive Therapy Unit in various stages of cardiovascular collapse, with or without an appreciation of the underlying condition by the referring clinician. In all these situations the patient is very likely to die, often with alarming rapidity, unless the anaesthetist has a clear understanding, not only of the disease itself, but also of the pharmacological techniques which may be used to control it.

Such is the rarity of phaeochromocytoma that an anaesthetist working in a General Hospital might never see a case in a lifetime of clinical practice. However, a specialist clinic to which hypertensive patients are referred from a wide geographical area may expect to diagnose several cases a year, and an associated department of surgical endocrinology will gain regular experience. In the centres achieving best results, anaesthetists are intimately concerned with all aspects of management.

THE ORIGIN AND INCIDENCE OF PHAEOCHROMOCYTOMA

Phaeochromocytomata develop in chromaffin cells derived from the primitive neural crest, at a variety of locations which stretch from the base of the skull to the anus. Most commonly they are found within the adrenal glands themselves, but some 6% are ectopic. Predominant among non-adrenal sites are the paravertebral sympathetic ganglia, especially those at the origin of the inferior mesenteric artery and aortic bifurcation, often known as the paraganglia of Zukercandl (van Heerden et al., 1982). Less commonly, they may occur in association with the cervical sympathetic chain (Gibbs et al., 1977). Tumours have been found to arise from sympathetic ganglia in the bladder wall, and a number of intrathoracic tumours have been described (McNeill, Groden and Neville, 1970; Besterman, Bromley and Peart, 1974; Wilson et al., 1974).

Phaeochromocytomata may be found in approximately 0.1% of hypertensive patients, but such is the progressive nature of the disease that it causes the deaths of some 1000 Americans each year (Hauptman, Modlinger and Ertel, 1983). In adults the commonest finding is a single adrenal tumour, with bilateral tumours in about 10% of cases. Some 30% are ultimately found to be malignant, and may give rise to catecholamine-secreting metastases. In children, 70% of tumours are bilateral, with a higher prevalence of extra-

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C. J. HULL, M.B. B.S., M.R.C.S., L.R.C.P., D.A., F.F.A.R.C.S., Department of Anaesthesia, Royal Victoria Infirmary, Newcastle Upon Tyne NE1 4LP.

adrenal sites than in adults, but a lower prevalence of malignancy (Kaufman et al., 1983).

Phaeochromocytomata occur as a recognized element of the Multiple Endocrine Adenoma (MEA) syndrome Type II (Sipple's syndrome), in which they present in association with medullary thyroid carcinoma, and are rarely solitary (Sipple, 1961; Carney, Sizemore and Tyce, 1975). One patient has been reported in whom phaeochromocytoma occurred in association with hypercalcitoninaemia and thyroid C-cell hyperplasia (Ram, Rao and Brown, 1978). Rarely, there may be some overlap with the Type I MEA syndrome, in which case patients may present with both phaeochromocytoma and pancreatic islet cell tumour (Tateishi et al., 1978).

It is also recognized that patients with the syndromes attributed to von Recklinghausen (multiple neurofibromatosis) and von Hippel-Lindau (cerebellar haemangioblastoma with retinal angioma) have a greatly increased prevalence of phaeochromocytoma (Bravo and Gifford, 1984).

CLINICAL PRESENTATION

Most commonly, patients are hypertensive and complain of headache, palpitations and excessive sweating. Only rarely are more than one of these symptoms absent. The hypertension may be either episodic or sustained; when episodic, attacks are often provoked by some particular activity or movement. A classic but unusual history is provided by the patient with a bladder-wall phaeochromocytoma who complains of intense headache and palpitations during or after micturition (Zimmerman, Biron and MacMahon, 1953; Messerli, Finn and MacPheo, 1982).

Many patients notice weight loss, anorexia and pallor, with cold hands and feet. In advanced cases the poor skin circulation can lead to marbling, mottling or even gangrene. There may be psychic changes ranging from mild anxiety to frank psychosis.

Some tumours are largely adrenaline-secreting, in which case the beta-adrenergic effects predominate (Page, Raker and Berberick, 1969). In these cases palpitations and tachyarrhythmias may be associated with a normal or even decreased arterial pressure (Northfield, 1967).

Very occasionally, phaeochromocytoma presents during pregnancy (Leak et al., 1977; Pinaud, Souron et al., 1985) and, until modern methods of management were adopted for these patients, the mortality was very high.

EFFECTS OF EXCESSIVE CATECHOLAMINE RELEASE

The uncontrolled release of catecholamines into the bloodstream leads to several important physiological changes which have great bearing on both diagnosis and clinical management. Indeed, the clinical presentation follows directly upon the catecholamine output of the tumour, which may be either episodic or sustained, and may consist of adrenaline and noradrenaline in widely differing proportions.

When the output consists predominantly of noradrenaline, long periods of vasoconstriction may lead to contraction of the venous pool, and marked reductions in circulating volume have been reported (Brunjes, Johns and Crane, 1960). Consequently, the abrupt administration of vasodilator drugs may cause the patient to develop the signs of acute hypovolaemia, as may removal of the tumour at operation. On the other hand, tumours secreting a relative excess of adrenaline are associated with tachycardia and tachyarrhythmias, but with less marked changes in arterial pressure and peripheral circulation.

Some patients are found to have an increased fasting blood glucose concentration with an abnormal tolerance curve, since high plasma catecholamine concentrations lead to glycogenolysis (fig. 1) and also inhibit insulin release by islet cells (Wilber, Turtle and Crane, 1966; Porte, 1967; Vance et al., 1969).

In fact, beta-adrenergic stimulation promotes insulin release, but the alpha effect is much more powerful, and predominates. Catecholamines also cause lipolysis, leading to increases in the plasma concentrations of free fatty acids, which provide alternative energy substrates and also impair the sensitivity to insulin. As a consequence, the patient may develop signs not unlike those of diabetes mellitus, and some patients have even become insulin-dependent (Duncan, Semans and Howard, 1944).

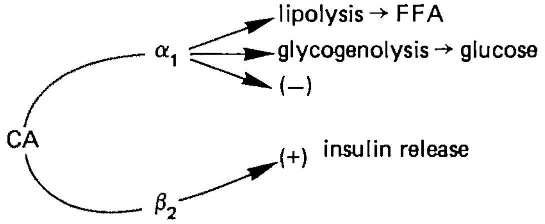

FIG. 1. Catecholamines increase blood glucose concentration by a combination of alpha effects, but reduce it by a beta effect. In most cases of phaeochromocytoma the alpha effect predominates.

Also, as a result of sustained catecholamine release, cardiomyopathy develops in some 20–30% of patients (Gilsanz et al., 1983). Histologically, the lesions have the appearance of myofibrillar degeneration and appear as small necrotic foci with interstitial infiltration with mononuclear leucocytes. The myocytes show characteristic contraction-band necrosis (van Vliet, Burchell and Titus, 1966). Later, areas of fibrosis and calcification may develop. Aetiological factors include a direct effect by high concentrations of catecholamines, coronary hypoperfusion, relative ischaemia as a result of increased oxygen demand, and increased platelet aggregation (Gonzalez-Campora et al., 1978).

PHAEOCHROMOCYTOMA CRISIS

If the effects of the release of catecholamine(s) remain uncontrolled, the patient will ultimately suffer a life-threatening crisis. This may be the result of predominantly pressor effects, in which case the presentation may resemble hypertensive encephalopathy, with neurological deficits, cortical blindness and finally unconsciousness (Radtke et al., 1975). The severe arterial spasm causes widespread underperfusion and impalpable peripheral pulses, leading to progressive metabolic acidaemia and death (McManus, Fleury and Roberts, 1981; Ouzts, 1982).

Alternatively, the patient may present with hypotension. This may be a "shock"-like syndrome developing following prolonged hypoperfusion, with multiple organ failure. Hypotension may also occur if the predominant catecholamine is adrenaline, in which case the patient may present in high-output cardiac failure (Baker et al., 1972). However, it is important to note that intense vasoconstriction may make indirect sphygmomanometry impossible, despite a normal or even increased central arterial pressure.

In all clinical presentations of phaeochromocytoma crisis the myocardial lesion plays a significant and, in some patients, a dominant role (Munk et al., 1977). The already damaged heart is less able to withstand very great increases in afterload, nor can it sustain high output during massive beta-adrenergic stimulation.

DIFFERENTIAL DIAGNOSIS

The history of an early case is often highly suggestive, but a firm diagnosis may require intensive investigation. The more advanced case often presents as a diffusely hypermetabolic state which may resemble thyrotoxicosis, diabetes mellitus, malignant hypertension, carcinoid syndrome, gram-negative septicaemia or diabetic precoma (Sjoerdsma et al., 1966). As stated above, the syndrome may present as a cardiomyopathy without hypertension.

When phaeochromocytoma occurs in pregnancy, it may resemble toxaemia at any stage from simple hypertension to frank eclampsia.

DIAGNOSTIC POINTERS

Catecholamines and metabolites

The plasma concentrations of adrenaline and noradrenaline may be assayed directly, and the daily output of their urinary metabolites may also be measured. Many previous authors have expressed their quantities by weight (ng ml^{-1} and mg/24 h), and this text adheres to the cited values. However, most British laboratories now express biochemical quantities in molar form, and table I indicates the relevant conversion factors. Where American authors have given quantities such as "total catecholamines" and "total metanephrines", exact conversion to molar quantities is impossible because of differing molecular weights.

Plasma catecholamine concentrations are the best single indicator, while urinary metabolites in isolation may show a greater proportion of false negatives. Conversely, many hypertensive patients in whom the diagnosis of phaeochromocytoma is suspected but not confirmed are found to have both plasma and urinary concentrations greater than the normal reference range (Brown et al., 1981).

In theory, hydroxy-methoxy-mandelic acid (HMMA), often mis-named vanillylmandelic acid (VMA), should be the most reliable, since it is the final common product of both catecholamine metabolic pathways (fig. 2). However, in practice, the intermediate metanephrines (MN) have proved to be better discriminators of phaeochromocytoma. All these measurements may vary

TABLE I. *Conversion factors*

	Mol. wt	1 mg =	1 mol^{-6} =
Adrenaline	183	5.46 mol^{-6}	0.183 mg
Noradrenaline	169	5.92 mol^{-6}	0.169 mg
Metanephrine	197	5.08 mol^{-6}	0.197 mg
Normetanephrine	183	5.46 mol^{-6}	0.183 mg
HMMA	199	5.02 mol^{-6}	0.199 mg

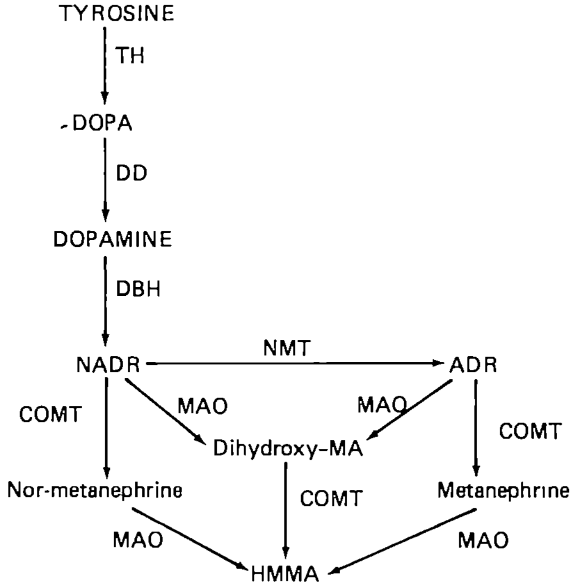

FIG. 2. Routes of synthesis and metabolism for adrenaline and noradrenaline, indicating the enzymes involved in each step. TH = Tyrosine hydroxylase; DD = dopa decarboxylase; DBH = dopamine beta-hydroxylase; NMT = n-methyl transferase; MAO = monoamine oxidase; COMT = catechol o-methyl transferase.

TABLE. II. *Expected concentrations of catecholamines and metabolites. *Values from Bravo and Gifford (1984)*

	Normal values	Range in 43 patients*
Urinary MN	< 1.3 mg/24 h	0.7–18 mg/24 h
Urinary HMMA	< 9.0 mg/24 h	3.0–50 mg/24 h
Plasma CA (ADR + NADR)	< 1 ng ml^{-1}	0.8–100 ng ml^{-1}

greatly with time and, therefore, should be made on a number of occasions. The concentrations to be expected are shown in table II.

Bravo and Gifford (1984) have emphasized the danger of reliance on any single test. Improved discrimination can be obtained by consideration of the concentrations of both plasma catecholamines and urinary metanephrines (fig. 3). Thus if a patient has a total plasma catecholamine concentration of less than 0.9 ng ml^{-1} and urinary metanephrine concentrations less than 1.8 mg/24 h, a diagnosis of phaeochromocytoma becomes unlikely.

Tests of catecholamine provocation and suppression

Early investigators made use of provocative tests to aid diagnosis in equivocal cases. The objective was to provoke catecholamine release,

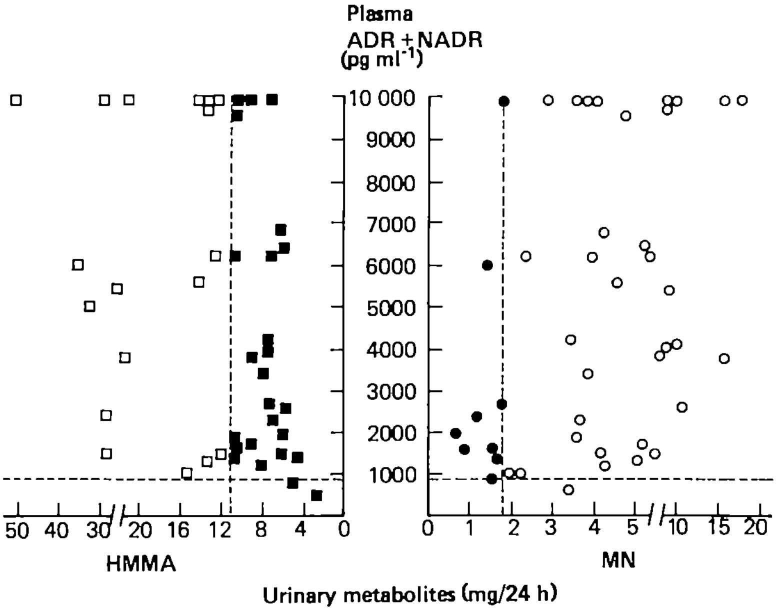

FIG. 3. Comparison of simultaneously measured concentrations of total plasma catecholamines, urinary HMMA and urinary metanephrines in 43 confirmed cases of phaeochromocytoma (Bravo and Gifford, 1984). The dashed lines indicate the 95% confidence limits for normal subjects. (Reproduced by permission of the authors.)

following which the positive case would develop a marked hypertensive "surge". Histamine or tyramine were the usual choice. However, both agents may provoke major hypertensive and tachyarrhythmic episodes in a patient with phaeochromocytoma, and the hazard to such a patient cannot be overemphasized.

Some modern authors (Bravo and Gifford, 1984) have advocated provocation by glucagon 2 mg in patients who are minimally hypertensive, followed by measurement of the plasma catecholamine concentrations and claim good discrimination without causing dangerous increases in arterial pressure or heart rate. Nevertheless, most British clinicians now take the view that, since a positive diagnosis can now be made without the use of provocative tests, they should never be contemplated.

An alternative approach is to suppress neurally-mediated catecholamine release, after which non-phaeochromocytoma patients with increased plasma catecholamine concentrations may be expected to show a reduction in plasma concentration, whereas positive cases will be unaffected.

The pentolinium test (Brown et al., 1981) suppresses noradrenaline output by means of a ganglion blocking agent. Plasma catecholamine concentrations are measured before and after pentolinium 2.5 mg i.v. The values in negative cases are reduced by 22–62%, in contrast to patients with phaeochromocytoma, in whom the concentrations remain greater than normal (fig. 4). This widely used test is a good discriminator between phaeochromocytoma and hypertension of other aetiology in which resting plasma catecholamine concentrations may be above the normal range.

The clonidine suppression test also depends upon blocking (with an alpha-2 agonist) neurogenically-mediated adrenal responses, such that, in normal individuals, the plasma catecholamine concentrations decrease, whereas patients with a phaeochromocytoma are unaffected (Bravo and Gifford, 1984). According to the authors, a decrease to less than 0.5 ng ml^{-1} excludes phaeochromocytoma.

In both tests it is essential that the catecholamine assay measures only free catecholamines in plasma, since conjugates can persist for hours and therefore may lead to a false positive diagnosis. It should also be noted that both pentolinium and clonidine may cause marked reductions in arterial pressure, especially in the case of patients receiving antihypertensive therapy.

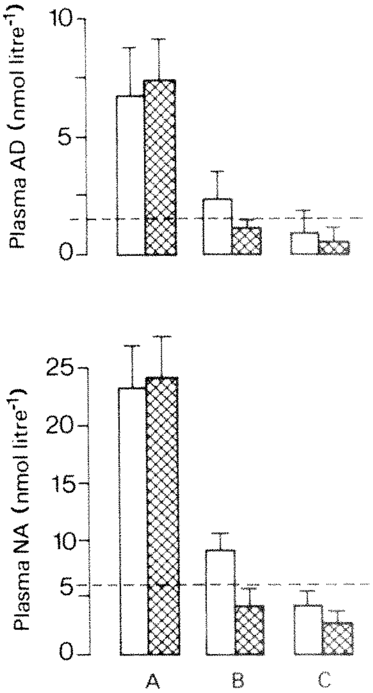

FIG. 4. The pentolinium suppression test (Brown et al., 1981). Open columns = before pentolinium; shaded columns = after pentolinium. Group A: Eighteen patients with phaeochromocytoma, in whom pentolinium did not suppress plasma catecholamine concentrations. Group B: Seven patients suspected of having phaeochromocytoma and undergoing selective venous sampling, in whom no tumour was found. Group C: Twelve patients who had intermittent increases in plasma concentration, but insufficient evidence to justify venous sampling. (Reproduced by permission of the authors.)

PHARMACOLOGICAL PROTECTION

As soon as the biochemical evidence is felt to be convincing, the patient must be protected from the hazards of uncontrolled catecholamine release. Then, imaging and surgical planning can proceed at a comfortable pace which ensures a successful outcome. Emergency surgery to remove a phaeochromocytoma from an unprepared patient should never be contemplated. Pharmacological control will be considered in detail in a later section.

TUMOUR LOCALIZATION

The relative proportions of adrenaline and noradrenaline in plasma may give some indication of the site of the tumour: if adrenaline is the predominant catecholamine then the tumour is very likely to be adrenal or Zuckercandl in origin (Page, Raker and Berberick, 1969).

A number of investigative procedures may be used to establish the precise location of the tumour(s). It is re-emphasized that they should not commence until the patient is protected from the dangers of uncontrolled catecholamine release.

Selective venous catheterization

Localization can be improved greatly by sampling blood directly from veins draining suspected tissues, and estimating catecholamine concentrations. From the pattern of concentrations in a variety of sites, the catecholamine "source" can often be deduced with some precision. Venous sampling is relatively non-invasive and non-provocative, and has been reported to be a successful discriminator in 97% of 31 cases (Allison et al., 1983). It is of greatest value in localizing single tumours.

Arteriography

In the past, arteriography played the major role in visualizing these tumours. However, injection of contrast medium may provoke marked release of catecholamine(s) leading to left heart failure and pulmonary oedema (Rouby et al., 1980).

Computerized axial tomography

Today, computerized axial tomography (CAT) has become the first line of attack following positive biochemical evidence, and may be expected to identify (fig. 5) at least 90% of tumours > 1 cm in diameter (Stewart et al., 1978). When used in conjunction with ^{131}I-meta-iodobenzyl guanidine scintigraphy (below), CAT imaging can be a powerful tool in localizing extra-adrenal tumours (Francis et al., 1983).

MIBG scintigraphy

Meta-iodobenzyl guanidine (MIBG) is a guanethidine derivative with structural similarities to noradrenaline, and is actively taken up into chromaffin storage granules. As may be expected, uptake is inhibited by reserpine, tricyclic antidepressants and phenylpropanolamine, but not by phenoxybenzamine or propranolol. MIBG has no known metabolic pathway, but is excreted in the urine. A proportion of MIGB will be concentrated into chromaffin tissue wherever situated, reaching optimal contrast with background tissue concentrations at 48–72 h. Thus if MIGB is labelled with iodine-131, chromaffin tissue can be imaged (fig. 6) using a gamma camera (Sisson et al., 1981). As a precaution against thyroid uptake by free iodine-131, patients are given potassium iodide before dosing. More recently, ^{123}I-MIBG has been used, having the advantages of shorter half-life and more efficient detection by a gamma camera.

Using doses up to 1 mCi of iodine-131, the procedure has proved highly effective in localizing both adrenal, ectopic and disseminated phaeochromocytomata (Sutton et al., 1982; Kalff, Kelly and McGrath, 1984; Thompson et al., 1984). A

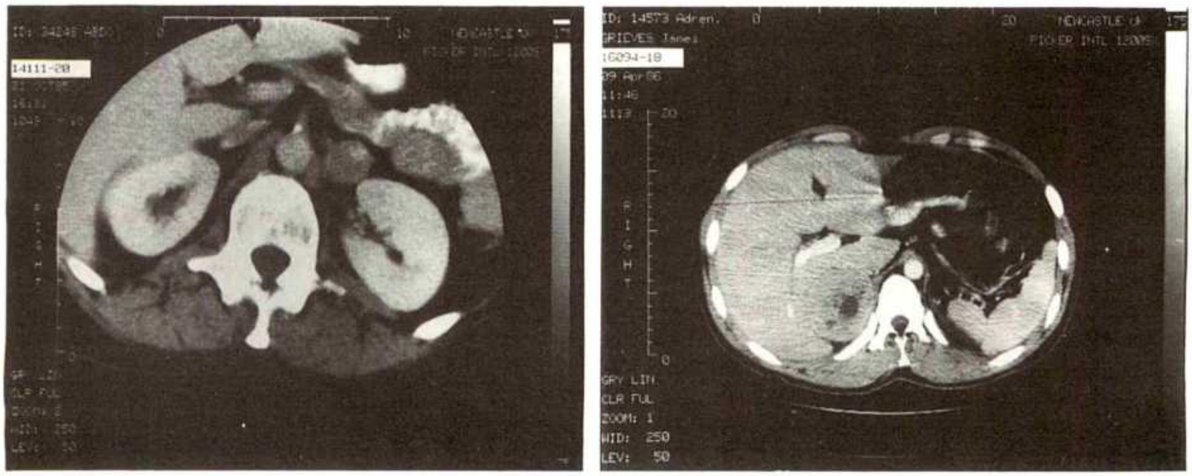

FIG. 5. Tumour localization by Computerized Axial Tomography. Left: CA tomogram of a 57-yr-old female patient to demonstrate the adrenal glands. The renal shadows are readily recognized, as is the wedge-shaped normal right adrenal. On the left side a 2-cm tumour lies medial to the kidney and lateral to the compressed left adrenal. Right: CA tomogram from a 17-yr-old male patient. An 8-cm tumour in which the interior shows signs of degeneration is clearly visible on the right side, extending upwards behind the liver. During subsequent surgical removal, control of tachycardia required 55 mg of propranolol.

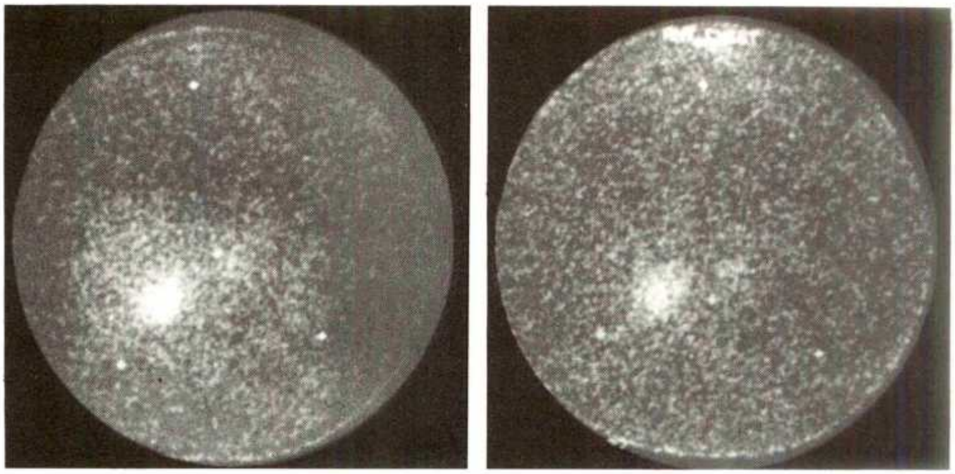

FIG. 6. Iodine-131 scintigrams of a patient with a right adrenal phaeochromocytoma, 56 h (left) and 5 days (right) after taking a tracer dose of ^{131}I-MIBG. The marker dots indicate the iliac crests and lumbar vertebrae. Concentration at the tumour site is clearly seen. There is also some concentration in the left adrenal site; this was considered normal, and the left gland appeared normal at operation. However, the patient presented with a left adrenal phaeochromocytoma some 2 years later.

small number of false-positive results have been reported, mostly as a result of concentration in normal adrenals (Brown, Fuller and Lavender, 1984; Gough et al., 1985). Conversely, some bladder tumours may be obscured by concentration of MIBG in the urine (*Lancet*, 1984).

PHARMACOLOGICAL CONTROL OF PHAEOCHROMOCYTOMA

Initial protection and stabilization

The principal step is to prevent the pressor effects of catecholamines, which reduce the circulating volume and increase the peripheral vascular resistance. This is best achieved by alpha-adrenergic blockade (Hoffman and Lefkowitz, 1980). Phentolamine and more recently phenoxybenzamine have been used widely for this purpose (Iseri, Henderson and Derr, 1951; Ross et al., 1967; Perry and Gould, 1972). Phenoxybenzamine is particularly useful since it has a long duration of action permitting twice-daily oral administration, and causes a non-competitive adrenergic blockade; thus surges of catecholamine release cannot "override" the inhibition as may occur with a competitive agent.

However, both drugs block not only post-synaptic alpha-1 receptors, but also pre-synaptic alpha-2 receptors (Hoffman and Lefkowitz, 1980). Since alpha-2 receptors are part of a negative-feedback loop which limits catecholamine release, alpha-2 antagonists lead to an *increase* in the release of noradrenaline at adrenergic terminals. Thus blockade of cardiac alpha-2 receptors leads to a secondary beta-adrenergic effect on both rate and contractile force of the heart, and the lack of negative feedback at alpha adrenergic sites must offset the degree of inhibition. It follows that they must be used with great caution in patients with marginal coronary perfusion with or without angina.

Prazosin has also been used successfully, with the claimed advantage of less tachycardia than phenoxybenzamine or phentolamine (Wallace and Gill, 1978; Cubeddu et al., 1982; Nicholson et al., 1983). Prazosin is a selective alpha-1 competitive adrenergic blocking agent. By sparing the presynaptic alpha-2 receptors, prazosin allows released noradrenaline to exert negative feedback, and thereby minimize secondary beta-adrenergic effects (Cambridge, Davey and Massingham, 1977; Colucci, 1982). As a result, tachycardia following prazosin treatment is much less marked than following phentolamine or phenoxybenzamine, and may be of particular value in managing patients in phaeochromocytoma crisis (Wallace and Gill, 1978). However, prazosin may cause a severe "first-dose" hypotensive effect as a result of a sudden decrease in afterload (Graham et al., 1976). The hypotensive effect is concentration-related (Bateman et al., 1979), and more pronounced than with other vasodilators (such as phenoxybenzamine) because secondary adrenergic effects do not occur.

Whichever alpha-antagonist is used, it must be introduced with caution, beginning with very small doses (for example, oral phenoxybenzamine 10 mg twice daily, or prazosin 1 mg 8-hourly). Dosage may be increased gradually as side effects recede, until all signs of pressor activity are suppressed. The daily doses required to suppress pressor activity may be considerable; the author has managed patients requiring phenoxybenzamine 300 mg daily, although 80–100 mg daily is more commonplace. Most patients can be controlled with prazosin 8–12 mg daily, although Nicholson and his colleagues (1983) have reported a patient whose hypertension was barely controlled by 16 mg daily. Initial side-effects are often very marked, and include postural hypotension, nausea, nasal stuffiness, blurred vision and general languor. As detailed above, phenoxybenzamine may cause tachycardia, so that prazosin is preferable when the tumour is predominantly adrenaline-secreting. However, prazosin may cause a severe initial hypotension, so that phenoxybenzamine is to be preferred for the initial control of hypertension when the patient is intensely vasoconstricted and the plasma volume reduced.

In opposition to the alpha-1 effect of noradrenaline, alpha-adrenergic blockade increases insulin output, but blood sugar is sustained (fig. 1) by other cathecholamine effects such as lipolysis and glycogenolysis (Wilkins, Schmidt and Doll, 1977).

When alpha-adrenergic blockade is established, tachycardia may be controlled by the cautious introduction of a beta-adrenergic antagonist. This should *never* be given until the pressor effects of the tumour are suppressed by alpha blockade, since antagonism of beta-mediated vasodilator effects (mostly in muscle) with unopposed alpha-mediated vasoconstriction may lead to severe pressor responses (Wark and Larkins, 1978). Furthermore, withdrawal of beta-stimulation from an already compromised myocardium may lead rapidly to acute pulmonary oedema (Sloand and Taylor Thompson, 1984). Propranolol has a wide spectrum of antagonism, and is generally preferred for initial control. In most cases, very modest doses (80–120 mg daily) are sufficient to maintain the heart rate within normal limits, but patients with predominantly adrenaline-secreting tumours may require up to 480 mg daily. Atenolol has a longer elimination half-time, and will provide "smoother" blockade when given twice daily. In patients whose hypertension and tachycardia are markedly episodic, these drugs may cause marked bradycardia between "surges". Here, a weak partial agonist such as oxprenolol may be more appropriate. Labetalol has been advocated as a first-line drug on the basis of having both alpha and beta-blocking effects (Rosei et al., 1976). However, the beta effect predominates, and there have been reports of pulmonary oedema following its use (Navaratnarajah and White, 1984).

It has been suggested that calcium channel blocking agents may have a useful role, since nifedipine has been shown to block cardiovascular responses to catecholamine surges in one patient (Lenders et al., 1985). However, reported experience with this line of management is, as yet, minimal.

Some patients have been reported to develop resistance to alpha-adrenergic blockade, and they may benefit from active suppression of catecholamine synthesis (Robinson et al., 1977). Patients in heart failure may also present a severe problem, in that alpha-blockade may lead to a worsening tachycardia, and the introduction of beta-blockade may then diminish cardiac performance even further. Here, also, it is worth considering active suppression of catecholamine synthesis.

Alpha-methyl-p-tyrosine (AMPT) inhibits tyrosine hydroxylase (fig. 2) and, therefore, blocks the rate-limiting conversion of tyrosine to dopa in the catecholamine synthetic pathway. AMPT can be given orally, gradually increasing the dose from 0.5 g day^{-1} up to a maximum of 4 g day^{-1}. This may be expected to reduce catecholamine synthesis by 40–80% (Engelman et al., 1968).

According to the published reports, AMPT is usually as effective in controlling the symptoms of phaeochromocytoma as receptor blocking agents, but in some cases spectacularly better (Sjoerdsma et al., 1965). Side-effects include diarrhoea, sedation, fatigue, anxiety or agitated depression, tremor and muscle stiffness. The CNS side-effects are possibly caused by dopamine depletion, but diarrhoea may be caused by a direct irritant effect on bowel mucosa. The current view is that AMPT is worth a trial in selected patients, and can be withdrawn if side-effects become unacceptable.

Early animal work showed that even low doses of AMPT caused crystalluria in dogs (Engelman and Sjoerdsma, 1966), but in the above human studies no crystalluria was observed with AMPT 4 g daily, but *was* seen at 5 g day^{-1}. It is estimated that at a dose of 4 g day^{-1}, crystalluria is unlikely when the urinary output remains greater than 2 litre/24 h.

Preoperative preparation

When the patient is pharmacologically protected from catecholamine excess and the tumour site has been identified, the preoperative phase begins. Until the need for preoperative preparation was appreciated, the operative mortality was as high as 30–45% (Apgar and Papper, 1951). In particular, removal of the tumour was often followed by a profound decrease in arterial pressure which could usually be restored by vasopressors (Kvale et al., 1957). However, the effects of these agents often declined progressively, leaving the patient in a state of intractable hypotension from which recovery was uncommon.

Following their observation that the circulating blood volume is decreased in many patients with phaeochromocytoma, Brunjes, Johns and Crane (1960) speculated that this may be the cause of post-excision hypotension. Later they suggested that preoperative alpha-blockade by phentolamine would correct this (Johns and Brunjes, 1962). Others have claimed that preoperative volume loading is more effective (Deoreo et al., 1974), but this approach is potentially hazardous since volume loading in the patient with poor myocardial reserve can precipitate congestive cardiac failure (Pinaud, Desjars et al., 1985).

In the experience of the author and many others, active interference with the circulating volume is quite unneccessary in the majority of patients, since the vasodilatation caused by sustained alpha-adrenergic blockade results in the spontaneous restoration of plasma volume. In the patient with diminished myocardial reserve, preoperative fluid loading may precipitate cardiac failure and should be avoided at all costs. It is desirable that all blood components are restored to normal, and 2–4 weeks should be allowed for the initial haemodilution to resolve.

As with initial control, phenoxybenzamine remains the first-choice vasodilator for the majority of patients. If the desired intensity of blockade cannot be achieved or maintained, then prazosin may be used in combination, and if necessary AMPT can be added in a low dose. If the tumour activity is controlled initially by AMPT alone, alpha-adrenergic blockade should not be omitted, since the partially suppressed tumour may still be capable of causing major pressor responses during surgery (Ram, Meese and Hill, 1985).

Beta-adrenergic blockade is of secondary importance in most patients, and is simply maintained at a level which will suppress tachycardia and palpitations. The patient with a predominantly adrenaline-secreting tumour may require more intense blockade, with very careful adjustment of the dose.

Echocardiography can be of value in both monitoring the improvement in myocardial function and evaluating the optimal timing of surgery (Mardini, 1981).

ANAESTHETIC TECHNIQUE

Since the first successful operation by the Swiss surgeon Roux in 1926, almost every possible anaesthetic technique has been advocated. However, this does not mean that all methods are equally effective, or even logical. A rational technique will be based firmly upon defined objectives and sound pharmacological principles rather than an idiosyncratic fondness for particular drugs or methods.

The anaesthetic objectives are to provide good surgical conditions in an unconscious relaxed patient, to avoid provocation of catecholamine release by anaesthetic drugs or manoeuvres, to suppress the adrenergic response to surgical stimulation, and to minimize the haemodynamic responses to both tumour handling and devascularization.

There can be no doubt that the best freedom from the adrenergic responses to surgery can be provided by regional anaesthesia, with or without a superimposed general anaesthetic, and this approach has been advocated (Cousins and Rubin, 1974). However, this approach provides no protection against the major problem of catecholamine release provoked by the handling of the tumour. Indeed, patients with extensive extradural blockade are often exquisitely sensitive to circulating catecholamines, and may be more rather than less difficult to manage at the critical stage. The author invariably uses a general anaesthetic technique.

Drugs to avoid

Today there is a wide choice of drugs, and it is logical to avoid those which have been firmly implicated in causing pressor responses or tachycardia.

Droperidol has been advocated by many

authors (Stamenkovic and Spierdijk, 1976; van Heerden et al., 1982; Vater, Achola and Smith, 1983; Desmonts and Marty, 1984; James, 1985; Pinaud, Desjars et al., 1985; Pinaud, Souron et al., 1985). However, it has been reported to cause pressor responses as a result of increased adrenal catecholamine release (Sumikawa and Amakata, 1977; Bittar, 1979), the mechanism involving inhibition of catecholamine re-uptake (Sumikawa et al., 1985).

Atropine inhibits the cardiac vagus and, therefore, potentiates the chronotropic effects of adrenaline. Although morphine has been used in a number of cases (Hamaji et al., 1984), histamine release may be expected to provoke catecholamine release from chromaffin granules. When more satisfactory drugs are available, its use would appear to be illogical.

Suxamethonium may stimulate sympathetic ganglia, and involuntary muscle fasciculation can provoke catecholamine release from the tumour (Stamenkovic and Spierdijk, 1976). One case report (Stoner and Urbach, 1968) described the provocation of a ventricular bigeminal rhythm by suxamethonium, and the authors speculated that this agent may provoke the release of catecholamine(s) by its action as a cholinergic agonist.

Tubocurarine and atracurium have both been shown to release histamine, and the provocation of a phaeochromocytoma by tubocurarine has been associated with at least one intraoperative fatality (Humble, 1967). Although atracurium has been used without incident in two reported cases (Stirt et al., 1985; Sheikh, 1986), it is better avoided.

Pancuronium is an indirect sympathomimetic agent which increases plasma catecholamine concentrations (Nana, Cardan and Domokos, 1973) and has been implicated in causing a severe pressor response in a patient with phaeochromocytoma (Jones and Hill, 1981).

Halothane has been advocated on the basis that it suppresses the catecholamine release associated with surgical stimulation (Cooperman, Engelman and Mann, 1967). However, catecholamine release following tumour handling is likely to be unaffected and its use for phaeochromocytoma removal has been associated with arrhythmias, presumably as a result of mycocardial sensitization to catecholamines (Etsten and Shimosato, 1965).

Drugs which may be safely used

Unlike some other opioids, fentanyl and alfentanil do not release histamine and both may be used freely. Alfentanil may be the drug of choice, having a very rapid onset of action, good vasodilating properties, and a shorter elimination half-time than other opioids.

Etomidate also releases no histamine and causes less cardiovascular disturbance than other induction agents. When it is used in sequence with potent opioids, pain on injection and involuntary muscle movements are not observed.

Enflurane has been used successfully (Kopriva and Eltringham, 1974; Ortiz and Diaz, 1975; Janeczko et al., 1977), and was regarded as the preferred agent in two recent reviews (van Heerden et al., 1982; Bravo and Gifford, 1984). Isoflurane has also been advocated on the grounds that arrhythmias are less easily provoked by circulating catecholamines than with other volatile agents (Johnston, Eger and Wilson, 1976), and has been shown to be a satisfactory agent (Fay and Holzman, 1983; Suzukawa et al., 1983; Conner, Miller and Katz, 1975).

Vecuronium does not provoke catecholamine release, does not release histamine, has no autonomic effects at clinical plasma concentrations, and is clearly the neuromuscular blocking agent of choice (Gencarelli et al., 1981).

There are no contraindications to the use of nitrous oxide.

A practical technique

The author's currently preferred technique is as follows (approximate doses for a 65-kg patient):

The last preoperative doses of alpha- and beta-adrenergic blocking drugs are given at 10 p.m. on the evening before surgery, based upon a starting time of 8.30 a.m. This schedule presents a patient with subtotal blockade, so that major catecholamine surges will continue to cause changes in arterial pressure, albeit within a safe range.

The patient is premedicated with temazepam 30 mg by mouth, given 2 h before arrival at the operating suite.

Arterial and venous cannulae are placed under local infiltration anaesthesia, and monitoring (radial artery pressure and ECG) established before induction.

Anaesthesia is induced using alfentanil 2 mg i.v., followed rapidly by vecuronium 8 mg and etomidate 15 mg. Controlled ventilation is established, the larynx is sprayed with 10% lignocaine and, 1 min later, intubation is performed with a pre-warmed Portex tracheal tube, and mechanical ventilation is established with humidified gases.

Following induction of anaesthesia, a central venous catheter is inserted and further monitoring channels established (CVP, capnograph, temperature, relaxograph). A pulmonary artery flotation catheter is not used routinely, despite Mihm's argument that, since these patients may have unsuspectedly poor myocardial reserve (Szakacs and Cannon, 1958), the CVP may not reflect left-sided filling pressures, even in apparently uncompromised patients (Mihm, 1983). Mihm (1983) urged the use of pulmonary artery catheters in all patients.

Pulmonary ventilation is adjusted to maintain the end-tidal $P_{A_{CO_2}}$ at 5.3 kPa. Anaesthesia is maintained with 35% oxygen in nitrous oxide, 1% enflurane and a continuing alfentanil infusion. This is given at 23 mg h^{-1} for 15 min and then maintained at 4 mg h^{-1} until the end of surgery. This regimen aims to maintain a plasma concentration of approximately 250 ng ml^{-1} during the maintenance phase. Neuromuscular blockade is maintained by repeated bolus doses of vecuronium, based upon neuromuscular transmission monitoring.

PHARMACOLOGICAL CONTROL OF CATECHOLAMINE RELEASE DURING SURGERY

As stated above, opioids, anaesthetic agents and neuromuscular blocking agents are used to suppress the adrenergic response to surgical stimuli. However, these conventional measures are quite inadequate when the tumour is handled, since plasma catecholamine concentrations may increase to very high values; in one patient they were reported to be 3700 times normal values (Suzukawa et al., 1983).

Control of hypertension

This is most effectively achieved by the i.v. infusion of a potent vasodilator so that, even under the influence of massive alpha- and beta-stimulation, dangerously high arterial pressures cannot be achieved. Widespread vasodilatation also restricts any catecholamine-driven increases in cardiac afterload and, therefore, minimizes increases in cardiac work. Even if large changes in systemic pressure do occur, indices of myocardial efficiency do not deteriorate and oxygen delivery to the tissues is sustained (Roizen et al., 1983).

Sodium nitroprusside (Csanky-Treels et al., 1976; van Heerden et al., 1982), phentolamine (Desmonts and Marty, 1984; Goldfein, 1963), nitroglycerin (McDonald, Doll and Reynolds, 1982), prazosin (Wallace and Gill, 1978), and magnesium sulphate (James, 1985) have all been advocated. Of these, sodium nitroprusside is currently the most widely used, although it must be accepted that avoidance of hypotension during periods of quiescence between catecholamine surges can present considerable difficulty.

Phentolamine is less satisfactory because tachycardia is an invariable problem, and tachyphylaxis may occur (El Naggar, Suerte and Rosenthal, 1977).

The use of magnesium sulphate (James, 1985) is based on the idea that calcium releases catecholamines from chromaffin tissue, and magnesium tends to do the opposite. It has also been suggested that magnesium alters the responsiveness of adrenergic receptors (Altura and Altura, 1981).

In principle, prazosin should be an effective drug for operative control, but some authors have reported difficulty with its use (Nicholson et al., 1983), possibly because of inadequate dosage. At present, as prazosin is commercially available in an oral preparation only, its use is limited to the preoperative phase of management.

Control of tachycardia

Conventially, tachycardia is controlled by means of beta-antagonists, often in high dosage. Although many patients have been managed successfully with propranolol, beta-adrenergic blockade is most logically provided by cardioselective agents such as practolol or atenolol, which will be less likely (*vide infra*) to cause postoperative hypoglycaemia than unselective agents (Deacon, Karunanayake and Barnett, 1977; Lager, Blohme and Smith, 1979).

In patients with evidence of cardiomyopathy, beta-adrenergic blockade has been shown to precipitate cardiac failure (Gilsanz et al., 1983; Ikram and Fitzpatrick, 1983), so that tachycardia and arrhythmias may be better controlled by other agents. For instance, ventricular ectopic beats are easily controlled with lignocaine (Gilsanz et al., 1983; Solares et al., 1986), which at low doses has less negative inotropic effects than beta-blockers. Amiodarone has been reported to be effective in controlling catecholamine-induced supraventricular tachycardias (Solares et al., 1986).

MANAGEMENT AFTER TUMOUR REMOVAL

At this stage the value of subtotal alpha-adrenergic blockade becomes apparent, since damped cardiovascular responses are observed when the exploring surgical hand encounters additional tumours or metastases.

When all chromaffin tissue has been isolated from the circulation, a modest fluid load is given rapidly (for example, 1 litre in 10 min) to offset the effects of abrupt catecholamine withdrawal. Blood losses are replaced immediately, and overall volume requirement is based upon the CVP responses to small fluid challenges. By the time skin closure is complete, the patient may be expected to be in a positive fluid balance of at least 1 litre.

Where severe blood loss is expected, or when the patient refuses transfusion, the use of a cell-saver might be considered logical. However, in one reported patient (Smith, Mihm and Mefford, 1983) severe post-excision hypertension was caused by very high catecholamine concentrations in the saver collection chamber, presumably as a result of blood scavenging during tumour handling.

MANAGEMENT OF THE POSTOPERATIVE PERIOD

IPPV is continued in the recovery or intensive therapy unit until spontaneous ventilation supervenes; the trachea is then extubated and, subsequently, the patient managed conventionally. However, there are several potential problems.

These patients are often very somnolent for the first 48 h after surgery, arguably as a result of the sudden removal of activating catecholamines and only gradually waning alpha-blockade. It is frequently found that opioid dose requirements are less than would be expected, and a conventional i.m. dose has been seen to cause severe respiratory depression.

If the alfentanil infusion is continued into the postoperative period the rate of administration can be titrated carefully against postoperative discomfort, thereby avoiding the peaks of respiratory depression following i.m. bolus doses of other opioids.

Volume replacement usually continues to exceed measured losses, possibly because of persisting alpha-blockade, and perhaps also a degree of vascular unresponsiveness to catecholamines (Bergman et al., 1978). The central venous pressure remains the best guide to volume requirement.

Some patients leave the operating theatre with no adrenocortical function, and require replacement therapy from the outset.

A number of patients have been found to be hypoglycaemic in the early postoperative period (Allen and Imrie, 1977; Martin, St-Pierre and Moliner, 1979; Chambers et al., 1982; Reynolds et al., 1983; Meeke, O'Keefe and Gaffney, 1985). This is thought (fig. 7) to be the result of insulin production by islet cells the output of which is no longer blocked by catecholamines, in response to hyperglycaemia caused by catecholamine surges and by sugar-containing i.v. fluids (Thomas and Alberti, 1978).

Further, it has long been known that stopping a catecholamine infusion causes a surge of insulin release (Cremer et al., 1971), and that the effect is intensified by the concurrent administration of non-selective beta-blockers such as propranolol (Porte, 1967).

In some patients, alpha adrenergic blockade prevents suppression of insulin output by catecholamines (Vance et al., 1969), but in others the effect may be partial (Reynolds et al., 1983) or even absent (Vance et al., 1969). After operation the lipolysis and glycogenolysis which had previously sustained the blood sugar are no longer present, so the blood glucose concentration can decrease to

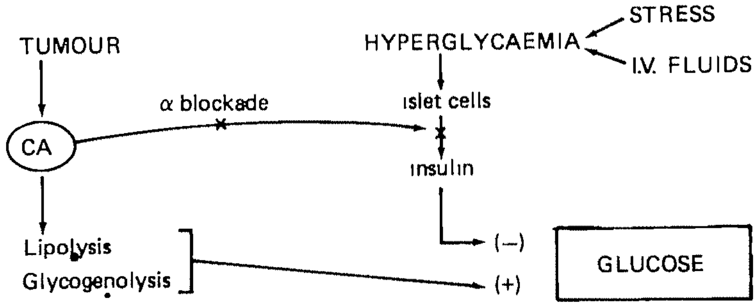

FIG. 7. Factors leading to hypoglycaemia after removal of a phaeochromocytoma.

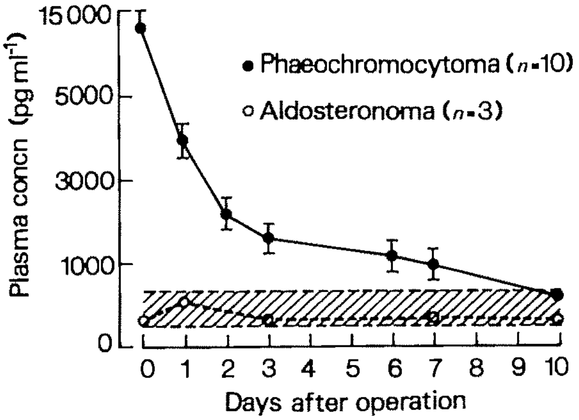

FIG. 8. Plasma total catecholamine concentrations after removal of a phaeochromocytoma (Bravo et al., 1979). Ten patients with phaeochromocytoma are compared with three with aldosteronoma, all patients undergoing adrenalectomy. The shaded area indicates the mean normal value ± 3 standard deviations. (Reproduced by permission of the authors.)

dangerously low values. It is important to note that persisting adrenergic blockade may mask the symptoms and signs of hypoglycaemia.

In some patients the arterial pressure does not return rapidly to normal after removal of the tumour. This may indicate a residual phaeochromocytoma (Ludmerer and Kissane, 1982), but in fact plasma catecholamine concentrations (fig. 8) may not decrease to normal values for several days after surgery (Bravo et al., 1979). This may be the result of the gradual release of sequestrated catecholamines, but the mechanism remains obscure.

MANAGEMENT OF THE INOPERABLE MALIGNANT PHAEOCHROMOCYTOMA

In some cases of malignant phaeochromocytoma it proves impossible to remove all active tissue. In this event the combined adrenergic blockade is continued into the postoperative period. Maintenance therapy then follows one or more of the following options:

(1) Maintenance adrenergic blockade with phenoxybenzamine and propranolol.

(2) Catecholamine synthesis suppression by alphamethyl-p-tyrosine (Engelman et al., 1968).

(3) ^{131}I-MIBG therapy (Ackery et al., 1984; Sisson et al., 1984). If ^{131}I-MIBG is given in high dose, sufficient radioactive iodine may be concentrated in the tumour to cause radio-necrosis. Attractive in principle, the material is very expensive (more than £1200 per 100-mCi dose, with three or four doses required) and the few patients treated to date have shown variable results.

(4) Tumour embolization with gelfoam (Hrabovsky et al., 1982).

CONCLUSION

Phaeochromocytoma remains one of the great challenges to anaesthetists in both operating theatre and intensive therapy unit. While perioperative deaths are now rare in the hands of clinicians to whom significant numbers of patients are referred, the condition continues to demand very great respect. The anaesthetist or surgeon to whom the very occasional patient is offered remains well advised to seek the assistance of an endocrine surgical unit, to whose surgeons and anaesthetists the problems are no less daunting, but have at least become familiar.

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MEGALOBLASTIC BONE MARROW CHANGES AFTER REPEATED NITROUS OXIDE ANAESTHESIA

Reversal with Folinic Acid

J. F. NUNN, I. CHANARIN, A. G. TANNER AND E. R. T. C. OWEN

SUMMARY

A seriously ill patient was found to have megaloblastic changes in his bone marrow after a nitrous oxide anaesthesia which lasted for 105 min. After an interval of 7 h a second nitrous oxide anaesthetic was administered, during which the patient received 30 mg of folinic acid. His marrow was normal when assessed 4 h later.

An 18-year-old male Sikh, who took a meat diet and was previously in normal health, sustained a deep penetrating stab wound in his left hypochondrium shortly before midnight as part of a stabbing affray in our District. At laparotomy by A.T. (2.15 a.m.), he was found to have a haemoperitoneum of 6 litre as a result of a divided mesenteric artery and a splenic capsular tear; there were also six perforations of the first loop of jejunum. A small bowel resection and splenectomy were performed. The anaesthetic included 70% nitrous oxide and lasted for 105 min. During the operation he received a total of 31 units of blood, 5 litre of Haemaccel, together with fresh frozen plasma and platelets. There were technical difficulties in the measurement of arterial pressure, but he had no palpable pulse for at least 30 min. He was returned to the Intensive Therapy Unit. His circulatory state remained unstable and because of persistent intra-abdominal bleeding it was decided to undertake a further laparotomy at 11.00 a.m. on the same day.

Amos and colleagues (1982) have reported an 89% mortality in 18 patients admitted to an intensive therapy unit with megaloblastic bone marrow changes following the administration of nitrous oxide. An abnormal deoxyuridine suppression (dU) test was observed in 11 of 13 patients who had received nitrous oxide for 2 h or less, and one of these patients was megaloblastic. Our patient had already received nitrous oxide for 105 min and a second administration could only aggravate inactivation of vitamin B_{12}. Nevertheless, nitrous oxide was an attractive choice of anaesthetic for a patient already paralysed and ventilated, but in an unstable circulatory state. It was considered that the patient's condition justified marrow puncture and this was carried out as soon as the second anaesthetic was induced.

Anaesthesia was induced by J.N. with nitrous oxide in oxygen at 11.15 a.m.; folinic acid 30 mg i.v. was given and anaesthesia continued for a total of 2 h. At the second laparotomy (E.O.), a further 5–6 litre of blood was found in the peritoneal cavity as a result of bleeding from the short gastric vessels. Bleeding points were secured and the abdomen closed. A second marrow puncture was undertaken 4 h after the second anaesthetic.

Recovery was uneventful and the trachea was extubated at midnight. Following surgery, the patient received folinic acid 30 mg daily for 5 days, during which his leucocyte count increased from 9.1 to 29.5×10^3 mm^{-3}. He left hospital 9 days after the second operation.

First bone marrow (11.30 a.m.)

This showed abnormal haemopoiesis of the type found in untreated pernicious anaemia (megaloblastic haemopoiesis). The dU suppression test was abnormal, the value being 18.4% (the upper limit of normal is 10% in our laboratory).

J. F. NUNN, M.D., PH.D., F.R.C.S., F.F.A.R.C.S., F.F.A.R.A.C.S. (HON.), F.F.A.R.C.S.I (HON.) (Division of Anaesthesia), I. CHANARIN, M.D., D.C.P., F.R.C.PATH. (Division of Haematology); Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ. A. G. TANNER, M.B., B.S., F.R.C.S.; E. R. T. C. OWEN, M.B., CH.B., F.R.C.S., F.R.C.S.I.; Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

Second bone marrow (5.30 p.m.)

This showed a restoration of normoblastic haemopoiesis and return to a normal dU suppression test (9.4%).

COMMENT

In the dU suppression test, marrow cells are incubated with deoxyuridine and the capacity of the marrow to methylate this to thymidine is assessed. The essential carbon donor is 5,10-methylene tetrahydrofolate, the concentration of which depends on normally functioning vitamin B_{12} and folate (Nunn and Chanarin, 1985). Normal marrow will meet more than 90% of its thymidine requirement by methylating uridine and, when ^{3}H-thymidine is added, less than 10% of the preformed thymidine is used. In contrast, when there is impaired thymidine synthesis in megaloblastic bone marrow, including that becoming megaloblastic as a result of nitrous oxide exposure, more than 10% of preformed ^{3}H-thymidine is incorporated.

The megaloblastic appearance of the marrow and the abnormal dU suppression test at the time of the second laparotomy leave little doubt that there was impaired methionine synthase activity as a result of oxidation of its co-factor, vitamin B_{12}, by the nitrous oxide. A second exposure to nitrous oxide would have made this worse, since inhibition of methionine synthase is rapid but recovery is slow (Deacon et al., 1980). However, the administration of folinic acid, a precursor of 5,10-methylene tetrahydrofolate, resulted in a normal marrow and dU suppression test a few hours after the second administration of nitrous oxide. Direct demonstration of inactivation of vitamin B_{12} would have required liver biopsy, which was not considered justifiable.

This patient provides confirmation of the observation by Amos and colleagues (1982) that administrations of nitrous oxide lasting for 2 h or less may result in impaired thymidine synthesis and megaloblastic bone marrow changes in seriously ill patients. In contrast, no changes were observed in relatively healthy patients receiving nitrous oxide for up to 6 h (O'Sullivan et al., 1981). We also confirm that folinic acid in appropriate dosage can offset the effect of nitrous oxide, with rapid restoration of a normal marrow. It has been found to be effective following exposure to nitrous oxide lasting 24 h (O'Sullivan et al., 1981; Skacel et al., 1982; Amos et al., 1984; Kano et al., 1984). This case illustrates the potential value of folinic acid for seriously ill patients who receive nitrous oxide repeated after a short interval.

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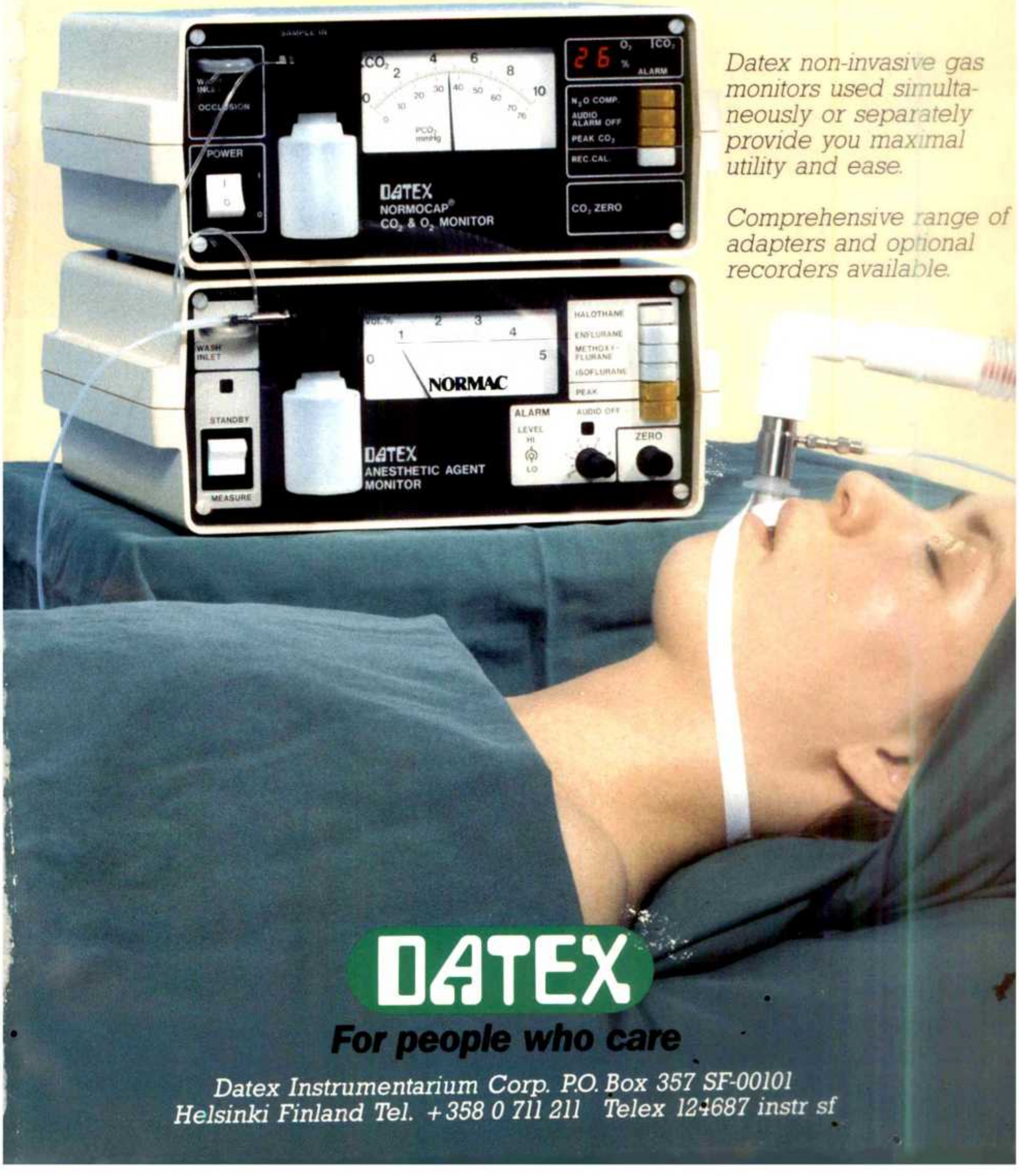

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